# Appendix 22b: 2009 Pharmacological study characteristics tables

**Please note that some of the references and the data in this appendix have been incorporated from the previous guideline and have therefore not been updated to reflect current house style.**

**Full terms of abbreviations are listed at the back of the guideline, except in some instances where they are explained in situ.**

**An asterisk next to an author's name indicates that their study is the primary study.**

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# Initial treatment with antipsychotic medication

**Characteristics of included studies (previous guideline)**

| Study | Methods | Participants | Interventions | Outcomes |
|---|---|---|---|---|
| **Emsley**<br><br>**1995** | Allocation: randomised - no further description.<br>Blindness: double - no further information.<br>Duration: 6 weeks.<br>Multicentre, multinational. | Diagnosis: first-episode schizophrenia/schizophre-niform disorder (DSM-III-R).<br>N=183.<br>Age: range 15-50.<br>Sex: male 122, female 61.<br>History: age at onset of illness, median 23 (risperidone), 24 years (haloperidol). | 1. Risperidone: dose mean 6.1mg/day, range 2-16mg. n=99.<br>2. Haloperidol: dose mean 5.6mg/day, range 1-16 mg. n=84.<br>Flexible dose regime for both groups. | Clinical improvement (>50% in total PANSS).<br>Global effect (CGI).<br>Mental state (BPRS - PANSS derived, PANSS).<br>Side effects (ESRS, specific reports).<br>Physiological monitoring (ECG, lab tests, body weight, vital signs).<br>Leaving the study early. |
| **Jones1998** | Allocation: random - no further details.<br>Blindness: double.<br>Duration: 54 weeks. | Diagnosis: schizophrenia.<br>N=65.<br>Setting: outpatient.<br>Multicentre.<br>Excluded if PANSS>90.<br>History: 'early phase' First 5 years of illness. | One month stabilisation phase followed by a one week washout, screening period.<br>1. Olanzapine: dose 5-20mg daily. n=21.<br>2. Risperidone: dose 4-10mg daily. n=21.<br>3. Haloperidol: dose 5-20mg daily. n=23. | Leaving the study early.<br><br>Unable to use -<br>Mental state (PANSS, no data).<br>Side effect (EPSRS, no data).<br>Cost (no data).<br>Cognitive function (CGI-S, neuropsychological test battery, no usable data). |

**References of included studies (previous guideline)**

**Emsley 1995**

Emsley RA, McCreadie R, Livingston M, De Smedt G, Lemmens P. (1995) Risperidone in the treatment of first-episode patients with schizophreniform disorder; a double-blind multicentre study. In: *8th European College of Neuro-psychopharmacology Congress*; 30 Sept - 4 Oct 1995; Venice, Italy.

**Jones 1998**

Jones B. (1998) Olanzapine versus risperidone and haloperidol in the treatment of schizophrenia. In: *151st Annual Meeting of the American Psychiatric Association;* 30 May - 4 June 1998; Toronto, Ontario.

**Characteristics of included studies (update)**

| **Study ID** | **DEHAAN2003** |
|---|---|
| **General info** | **Funding source:** Non-industry support |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** Observed case |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment: *6* |
| | **Raters:** Not stated to be independent of treatment |
| | **Design:** Single-centre Academic Medical Centre in Amsterdam, Netherlands |
| | **Number of people screened, excluded & reasons:** Not reported |
| | **Notes about study methods:** Randomisation procedures not reported |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 100% |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:**<br>- Aged 17-28<br>- DSM-IV criteria for schizophrenia |
| | **Exclusion criteria:**<br>- Neurological or endocrine disease<br>- Mental retardation<br>- Use of adjunctive medications such as mood stabilisers or antidepressants<br>- History of clozapine treatment<br>- History of unresponsiveness to haloperidol or clozapine |

- IM antipsychotic treatment in past year

**Total sample size:** No. randomised: 24

**Total sample size:** ITT population: Unclear

**Age:** Range *17-26*

**Ethnicity:** Not reported

**Setting:** Inpatient

**History:**
Duration of illness: 4-40 months
Number of psychotic episodes: 1-2

**Baseline stats:** No significant difference between groups

**Interventions** **Intervention - group 1.:** Olanzapine, 7.5mg/day; n=12

**Intervention - group 2.:** Haloperidol, 2.5mg/day; n=12

**Notes about the interventions:** Only oxazepam for anxiety or insomnia was allowed as adjunctive medication

**Outcomes** **Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Leaving the study early:** Leaving because of adverse effects

**Global state & service outcomes (e.g. CGI):** Average score/change in global state - CGI

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS, MADRS

**Adverse events:** Average score/change in specific adverse effects - BAS, SAS

**Quality of Life:** Average score/change in quality of life - Subjective wellbeing

**Other:** Neuroimaging (D2 receptor occupancy)

**Quality** **1.1 The study addresses an appropriate and clearly focused question.:** Adequately addressed

**1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately

**1.3 An adequate concealment method is used.:** Not addressed

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Adequately addressed

**1.5 The treatment and control groups are similar at the start of the trial.:** Adequately addressed

**1.6 The only difference between groups is the treatment under investigation.:** Well covered

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Adequately addressed

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** <20%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Not addressed

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not applicable

**2.1 How well was the study done to minimise bias?: +**

| **Study ID** | **LEE2007** |
|---|---|
| **General info** | **Funding source:** Non-industry support<br>**Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial<br>**Type of analysis:** Completer<br>**Blindness:** Double-blind<br>**Raters:** Independent of treatment<br>**Design:** Multi-centre - Two centres in Taipei, Taiwan<br>**Number of people screened, excluded & reasons:** Number screened not reported.<br><br>The study consisted of 95 healthy controls and 68 patients with schizophrenia. Out of the 68 patients, 20 were drug-naive<br>**Notes about study methods:** The drug-naive patients were randomly divided into two groups. Randomisation procedure not reported.<br><br>Results are reported for the 20 drug-naive participants only. The total schizophrenia sample was only compared to the healthy controls to demonstrate that the tests used in the study indicate significant cognitive deficits in patients with schizophrenia. |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 100%<br>**Diagnostic tool:** DSM-IV<br>**Inclusion criteria:**<br>- PANSS Score > 65<br>**Total sample size:** No. randomised 68 (20 of these were drug-naive).<br><br>The study also included 95 healthy controls<br>**Gender:** % female 44% |

All controls were male

**Age:** Mean 32.6(1.0)

**Ethnicity:** Not reported

**Setting:** Inpatient

**Baseline stats:**
Baseline of drug-naive participants
[Haloperidol / Risperidone]
PANSS total: 89.5(4.8) / 94.2(3.1)

**Notes about participants:** The drug-naive participants had no previous history of other functional psychosis, neurological illness, substance abuse within the past 2 years, history of substance dependence, ECT within the past 6 months, or any significant medication conditions.

**Interventions** **Intervention - group 1.:** Haloperidol, mean dose = 7.6(2.6)mg/day; n=10

**Intervention - group 2.:** Risperidone, mean dose = 4.9(2.1)mg/day; n=10

**Notes about the interventions:**
Both subgroups of patients initially received a low dose of antipsychotic drug which was gradually titrated up to higher dosage over the course of the study.

No additional antipsychotic medication and mood stabilisers were permitted. Patients received benzodiazepines based on individuals' psychiatric syndrome if required.

**Outcomes** **Leaving the study early:** Leaving because of adverse effects

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS

**Adverse events:** Average score/change in specific adverse effects - AIMS

**Cognitive functioning:** Average score/change in cognitive functioning - WCST; Maze task

**Quality** **1.1 The study addresses an appropriate and clearly focused question.:** Adequately addressed

**1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately

**1.3 An adequate concealment method is used.:** Not addressed

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered

**1.5 The treatment and control groups are similar at the start of the trial.:** Adequately addressed

**1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Adequately addressed

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was**

**completed?:** <20%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Poorly addressed

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not addressed

**2.1 How well was the study done to minimise bias?:** +

| **Study ID** | **LIEBERMAN2003A** |
|---|---|
| **General info** | **Funding source:** Pharmaceutical industry |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** ITT Patients were included in the efficacy analyses only if they had a baseline measure and at least one post-baseline measure |
| | **Type of analysis:** LOCF Also used mixed-models analysis |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment 24 weeks - first 12 weeks reported here |
| | **Raters:** Not stated to be independent of treatment |
| | **Design:** Multi-centre - 14 medical centres in North America and Western Europe |
| | **Number of people screened, excluded & reasons:** 263 randomised, 244 completed baseline assessment, 167 completed endpoint assessment and included in analysis |
| | **Notes about study methods:** Randomisation procedures not reported |
| **Participants** | **Diagnosis:** Other schizophrenia related [%] 8% schizoaffective, 27% schizophreniform |
| | **Diagnosis:** Schizophrenia [% of sample] 65% |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:**<br>- Aged 16-40<br>- Onset of psychotic symptoms before age 35 years<br>- Met DSM-IV criteria for schizophrenia, schizophreniform or schizoaffective disorder<br>- Experienced psychotic symptoms for >=1 month but not more than 60 months<br>- Score >=4 on at least two PANSS psychosis items or >=5 on one psychosis item |

- CGI score >=4 (moderately ill)
- Required treatment with antipsychotics on a clinical basis
- Level of understanding sufficient to communicate with research staff and to cooperate with all tests and examinations required by protocol
- Understood nature of the study and gave informed consent
- If female and of childbearing potential, using a medically accepted means of contraception

**Exclusion criteria:**
- Lifetime history of antipsychotic treatment for >=16 cumulative weeks
- Lifetime history of clozapine treatment
- Treatment with an injectable depot antipsychotic within less than 3 dosing intervals prior to study
- Pregnant or nursing
- Serious unstable illness or findings from a medical examination suggesting a contraindication to antipsychotic drug treatment
- History of allergic or severe reactions to study medications
- DSM-IV substance dependence within past month
- Judged to have serious suicide risk
- Requiring treatment with anticonvulsants, benzodiazepines (except for amelioration of agitation or EPS), antidepressants, stimulants or other antipsychotics used concurrently with study medication
- Contraindication to neuroimaging (e.g. having metal prostheses)
- History of any DSM-IV psychotic disorder with recovery
- Premorbid IQ <=70
- Received ECT within past month.

**Total sample size:** No. randomised *263*

**Total sample size:** ITT population *167*

**Gender:** % female 16%

**Age:** Mean 23.9 (4.6)

**Ethnicity:**
Caucasian: 50%
African descent: 39%
East/Southeast Asian: 3%
Western Asian: 1%
Hispanic: 5%
Other: 2%

**Setting:** Outpatient

**Setting:** Inpatient

**History:**
[Olanzapine / Haloperidol]
Days of illness: 360.8 (337.1) / 513.3 (424.1)
Days previous antipsychotic use: 41.6 (53.9) / 42.7 (99.1)
No previous antipsychotic use: 21% / 35%

**Baseline stats:**
[Olanzapine / Haloperidol]
PANSS: 80.83 (14.30) / 81.90 (15.60)

**Notes about participants:** Included only patients with a first-episode of psychosis

**Interventions** **Intervention - group 1.:** Olanzapine, mean 9.1 mg/day, n = 131

**Intervention - group 2.:** Haloperidol, mean 4.4 mg/day, n = 132

**Outcomes** **Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Leaving the study early:** Leaving because of adverse effects

**Global state & service outcomes (e.g. CGI):** Average score/change in global state

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS; Montgomery-Åsberg Depression Rating Scale

**Mental state (e.g. BPRS, PANSS, BDI):** Clinically significant response in mental state - Patients who met the following criteria, defined a priori, were classified as treatment responders: 1) had no rating of >3 (mild) on items P1, P2, P3, P5, and P6 of the Positive and Negative Syndrome Scale, and 2) had a ≥30% reduction from baseline in the Positive and Negative Syndrome Scale total score, and 3) had a CGI severity score ≤4 (moderately ill)

**Adverse events:** Number of people with specific adverse effects - Vital signs (blood pressure, pulse, weight, and temperature) were measured at each study visit. Side effects were recorded by using the Coding Symbols for a Thesaurus for Adverse Reaction Terms (COSTART) classification terms at each assessment visit. Extrapyramidal signs and abnormal involuntary movements were assessed by examinations of patients and scored on the Simpson-Angus Rating Scale (including an additional dystonia item), the Abnormal Involuntary Movement Scale, and the Barnes Rating Scale for Drug-Induced Akathisia at every assessment visit

**Quality** **1.1 The study addresses an appropriate and clearly focused question.:** Well covered

**1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately

**1.3 An adequate concealment method is used.:** Not addressed

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered

**1.5 The treatment and control groups are similar at the start of the trial.:** Well covered

**1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** 20-50%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Adequately addressed

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not addressed

**2.1 How well was the study done to minimise bias?:** +

| **Study ID** | **MCEVOY2007A** |
|---|---|
| **General info** | **Funding source:** Pharmaceutical industry |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** ITT : Modified ITT population defined as patients who were randomly assigned to a treatment and returned for at least one post-randomisation assessment. |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment *52* |
| | **Raters:** Not stated to be independent of treatment |
| | **Design:** Multi-centre - US and Canada (details from www.ClinicalTrials.gov) |
| | **Number of people screened, excluded & reasons:** Not reported |
| | **Notes about study methods:** Randomisation procedure not reported |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 57.8% |
| | **Diagnosis:** Other schizophrenia related [%] Schizophreniform disorder - 28.8%<br>Schizoaffective disorder - 13.5% |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:**<br>- consenting patients aged 16-40 meeting DSM-IV criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder.<br>- had to be in first-episode of their psychotic illness and had to be continuously ill for >=1month and no more than 5 months<br>- PANSS >-4 on at least one psychotic item<br>- CGI-S >=4<br>- female participants of child-bearing potential had to be using a medically acceptable form of contraceptive |

**Exclusion criteria:**
- prior psychotic episode had remitted for >=3 months, or if they had prior antipsychotic drug treatment for >16 cumulative weeks
- not speaking English
- history of mental retardation
- pregnant or nursing
- serious unstable medical condition, or a known allergy to one of the study medications
- participated in an investigational drug trial within 30 days before first treatment visit.

**Total sample size:** ITT population Unclear

**Total sample size:** No. randomised *400*

**Gender:** % female 27%

**Age:** Mean *24.5(5.8)*

**Age:** Range *16*.4 - 44.4

**Ethnicity:**
White - 51.3%
Black - 43.0%
Other - 5.8%

**Setting:** Inpatient

**Setting:** Outpatient

**Setting:** Emergency department services for the evaluation and treatment of psychosis

**History:**
[Olanzapine / Quetiapine / Risperidone]
Age of onset: 23.4(5.3) / 23.9(5.7) / 23.0(5.7)
Duration of illness, months: 11.0(12.86) / 15.1(20.04) / 12.7(17.90)
Inpatient treatment, n(%): 29(21.8) / 29(21.6) / 26(19.7)
Illness onset >60 months before baseline, n(%): 1(0.8) / 4(3.1) / 4(3.2)

**Baseline stats:**
[Olanzapine / Quetiapine / Risperidone]
PANSS total: 74.3(16.27) / 74.2(15.15) / 73.0(15.94)
CGI: 4.3(0.75) / 4.3(0.69) / 4.2(0.85)

**Notes about participants:**[Olanzapine / Quetiapine / Risperidone]
Antipsychotic naive, n(%), 32(24.2) / 36(26.9) / 28(21.1)
Age >40, n(%): 3(2.3) / 2(1.5) / 2(1.5)
Mean duration of previous antipsychotic use, weeks: 6.9(8.81) / 6.6(7.34) / 5.4(4.97)

Previous antipsychotic treatment >=16weeks total, n(%) : 7(7.1) / 6(6.1) / 3(2.9)

**Interventions** **Intervention - group 1.:** Olanzapine, 2.5-20mg/day, mean dose = 11.7(5.3) mg/day; n=133

**Intervention - group 2.:** Quetiapine, 100-800mg/day, mean dose = 506(215) mg/day ; n=134

**Intervention - group 3.:** Risperidone, 0.5-4mg/day, mean dose = 2.4(1.0) mg/day; n=133

**Notes about the interventions:**
On days 1 and 2, all patients received one capsule of Olanzapine (2.5mg), Quetiapine (100mg) or risperidone (0.5mg) in the evening. At the treating physician's discretion, the dose could be increased by one capsule every other day, up to a maximum of four capsules twice daily.

Any previous antipsychotic therapy was tapered and discontinued during the first 2 weeks and no subsequent use of antipsychotic was permitted.

Treatment with an adjunctive antidepressant or mood stabiliser during the first 8 weeks of treatment was not allowed unless approved by the project medical officer.

Anticholinergics were permitted for up to a total of 2 weeks over the course of the trial.

**Outcomes** **Death:** Suicide, suicide attempts, alleged homicide, completed suicides and suicidal ideation

**Leaving the study early:** Leaving because of adverse effects

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Global state & service outcomes (e.g. CGI):** Clinically significant response in global state - CGI - clinical response defined as a score <=3 on CGI-S item at any time during the trial

**Global state & service outcomes (e.g. CGI):** Average score/change in global state - CGI

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS

**Adverse events:** Number of people with general adverse effects

**Adverse events:** Average score/change in specific adverse effects - BAS; SAS; AIMS

**Adverse events:** Number of people with specific adverse effects - Main AEs reported were day-time drowsiness, weight gain, insomnia, increased sleep hours, menstrual irregularities and dry mouth.

**Quality of Life:** Average score/change in quality of life - Heinrichs-Carpenter QoL scale

**Other:** Weight Change; BMI; metabolic measures including triglyceride and cholesterol levels; Prolactin levels; Calgary Depression Scale

**Quality** **1.1 The study addresses an appropriate and clearly focused question.:** Well covered

**1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately

**1.3 An adequate concealment method is used.:** Not addressed

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered

**1.5 The treatment and control groups are similar at the start of the trial.:** Well covered

**1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** >50% primary outcome of study was to assess treatment discontinuation.

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Adequately addressed

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not addressed

**2.1 How well was the study done to minimise bias?:** +

| **Study ID** | **MOLLER2008** |
|---|---|
| **General info** | **Funding source:** Non-industry support *German Ministry of Education and Research* |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** ITT - The intent-to-treat (ITT) sample comprised all randomized patients except those whose initial diagnosis had been revised (n = 5, RIS; n = 2, HAL). |
| | **Type of analysis:** LOCF |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment 8 weeks |
| | **Raters:** Not stated to be independent of treatment |
| | **Design:** Multi-centre 13 German psychiatric hospitals |
| | **Number of people screened, excluded & reasons:** 1372 assessed for eligibility (22% included in acute study) |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] Besides fulfilling the criteria for schizophrenia according to ICD-10 F20, 289/302 (95.70%) patients also fulfilled the respective DSM-IV criteria. |
| | **Diagnostic tool:** ICD-10 |

**Inclusion criteria:**
- acute manifestation of FES according to ICD-10 F20 criteria;
- age 18–60 years;
- adequate proficiency in German;
- no involuntary in-patient treatment (at the date of inclusion);
- written informed consent.

**Exclusion criteria:**
- pregnancy;
- insufficient response to pretreatment with risperidone or haloperidol;
- other contraindications for risperidone or haloperidol;
- mental retardation ;
- organic brain disease;
- substance abuse;
- history of suicidal behaviour;
- severe physical disease ;
- participation in other trials.

**Total sample size:** No. randomised 296

**Total sample size:** Safety population 143 (RIS); 146 (HAL)

**Total sample size:** ITT population 143 (RIS); 146 (HAL)

**Gender:** % female 40.5%

**Age:** Mean 30.1 (9.8)

**Setting:** Inpatient

**Baseline stats:** PANSS = 77.3 (23) RIS; 80.8 (24.8) HAL

**Interventions** **Intervention - group 1.:** RIS, mean dose 3.8 (1.5) mg/d

**Intervention - group 2.:** HAL, mean dose 3.7 (1.5) mg/d

**Outcomes** **Leaving the study early:** Leaving because of adverse effects

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Global state & service outcomes (e.g. CGI):** Average score/change in global state CGI-S

**Mental state (e.g. BPRS, PANSS, BDI):** Clinically significant response in mental state

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS, GAF, HDRS

**General and psychosocial functioning (e.g. SFS):** Average score/change in general functioning - SOFAS

**Adverse events:** Number of people with specific adverse effects - SAS, AIMS, HAS

| | |
|---|---|
| **Quality** | **1.1 The study addresses an appropriate and clearly focused question.:** Well covered |
| | **1.2 The assignment of subjects to treatment groups is randomised.:** Well covered |
| | **1.3 An adequate concealment method is used.:** Well covered |
| | **1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered |
| | **1.5 The treatment and control groups are similar at the start of the trial.:** Well covered |
| | **1.6 The only difference between groups is the treatment under investigation.:** Well covered |
| | **1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered |
| | **1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** >50% |
| | **1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Adequately addressed |
| | **1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not addressed |
| | **2.1 How well was the study done to minimise bias?:** ++ |

| | |
|---|---|
| **Study ID** | **SCHOOLER2005** |
| **General info** | **Funding source:** Pharmaceutical industry |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** ITT All randomised participants that received study medication |
| | **Blindness:** Double-blind |
| | **Duration:** Median duration:<br>Risperidone: 192 days<br>Haloperidol: 218 days |
| | **Duration:** No. weeks of treatment 104 |
| | **Raters:** Not stated to be independent of treatment |
| | **Design:** Multi-centre 11 countries |
| | **Number of people screened, excluded & reasons:** 559 randomised, 4 did not receive study medication and were excluded from analysis; a further 21 were excluded from efficacy analyses due to violations of good clinical practice. |

**Notes about study methods:** Randomisation balanced by site

**Participants**

**Diagnosis:** Schizophrenia [% of sample]
[Risperidone / Haloperidol]
Schizophrenia: 55% / 42%

**Diagnosis:** Other schizophrenia related [%]
[Risperidone / Haloperidol]
Schizoaffective: 6% / 9%
Schizophreniform: 39% / 49%

**Diagnostic tool:** DSM-IV

**Inclusion criteria:**
- Age 16-45
- DSM-IV schizophrenia, schizophreniform disorder or schizoaffective disorder that has lasted <1 year, during which there were no more than two psychiatric hospitalisations for psychosis
- <=12 weeks cumulative exposure to antipsychotics
- Required antipsychotics at entry.

**Exclusion criteria:**
- Any other DSM-IV axis I diagnosis including substance abuse or dependence
- Needing another non-antipsychotic psychotropic medication at entry
- Serious or unstable mental illness.

**Total sample size:** No. randomised 559

**Total sample size:** Safety population 555

**Gender:** % female Risperidone: 29%; Haloperidol: 28%

**Age:** Mean 25

**Ethnicity:** White 74%
Black 13%
Hispanic 3%
Other 10%

**History:**
[Risperidone / Haloperidol]
No previous antipsychotic exposure: 34% / 28%
Age at first onset of psychotic symptoms
Males: 22.89 (6.49) / 23.86 (6.43)
Females: 25.33 (7.66) / 25.71 (7.71)

**Baseline stats:** PANSS Total
Risperidone: 83.7 (SE 1.24)
Haloperidol: 81.1 (SE 1.23)

**Interventions** **Intervention - group 1.:** Risperidone, mean model dose = 3.3 mg/day; n=278

**Intervention - group 2.:** Haloperidol, mean modal dose = 2.9 mg/day; n=277

**Notes about the interventions:**
3-7 day washout phase (waived for extremely ill patients)

At the start of treatment phase, once daily dose of 1mg, which could be increased to 2mg/day on Day 4 and thereafter by 1mg each week, up to max 4mg/day. In exceptional cases (i.e. insufficient response with at most mild EPS at 4mg), this could be increased further by 1mg each week up to 8mg max.

Concomitant psychotropic medications were allowed for addressing EPS; chloral hydrate, zolpidem, or flurazepam for sleep and lorazepam for agitation.

**Outcomes** **Death:** Suicide Ideation, completed suicides

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Global state & service outcomes (e.g. CGI):** Relapse defined as 1. >=25% increase on PANSS (or 10-point increase if baseline score <=40), 2. CGI change rating of "much worse" or "very much worse", 3. deliberate self-harm, 4. clinically significant homicidal or suicidal ideation, or completed suicide, 5. violent behaviour resulting to significant damage to other individuals or property.

**Global state & service outcomes (e.g. CGI):** Average score/change in global state CGI

**Mental state (e.g. BPRS, PANSS, BDI):** Clinically significant response in mental state Clinical improvement defined as >=20% decrease on PANSS total score

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state PANSS

**Adverse events:** Number of people with specific adverse effects Prolactin-related AEs, use of concomitant medications (anticholinergics, benzodiazepines, beta-blockers)

**Adverse events:** Average score/change in specific adverse effects Extrapyramidal Symptoms Rating Scale

**Other:** Weight gain, vital signs, ECG parameters, max prolactin levels

**Quality** **1.1 The study addresses an appropriate and clearly focused question.:** Well covered

**1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately

**1.3 An adequate concealment method is used.:** Not addressed

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Adequately addressed

**1.5 The treatment and control groups are similar at the start of the trial.:** Well covered

**1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** 20-50%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Well covered

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not reported adequately

**2.1 How well was the study done to minimise bias?:** +

**Study ID** **VANNIMWEGEN2008**

**General info** **Funding source:** Pharmaceutical industry

**Published or unpublished data?:** Published

**Method** **Type of study:** Individual randomised trial

**Type of analysis:** LOCF

**Type of analysis:** ITT included all those who had received at least one dose of study drug and had at least one follow-up assessment.

**Blindness:** Double-blind

**Duration:** No. weeks of treatment 6

**Raters:** Not stated to be independent of treatment

**Design:** Multi-centre 4 mental health centres in the Netherlands.

**Number of people screened, excluded & reasons:** 201 assessed for eligibility, 54 refused to participate, 9 were excluded due to other reasons

**Notes about study methods:** Randomisation procedure not reported

**Participants** **Diagnosis:** Schizophrenia [% of sample] Not stated

**Diagnosis:** Other schizophrenia related [%] Not stated

**Diagnostic tool:** DSM-IV

**Inclusion criteria:**
- In and outpatient with a diagnosis of schizophrenia, schizoaffective disorder or schizophreniform disorder.
- Young adults with recent onset schizophrenia
- Aged 18-30

**Exclusion criteria:**

- Concomitant use of any other antipsychotic drug (not olanzapine or risperidone)
- Depot antipsychotic medication 3 months prior to inclusion
- Current use of other psychotropic medications (exception: oxazepam or biperiden)

**Total sample size:** No. randomised 138

**Total sample size:** ITT population 128

**Gender:** % female 20

**Age:** Mean 25

**Ethnicity:** Not reported

**Setting:** Inpatient

**Setting:** Outpatient

**History:** Not reported

**Baseline stats:** Not reported

**Interventions**

**Intervention - group 1.:** Olanzapine, 5-20mg/day; N = 66

**Intervention - group 2.:** Risperidone, 1.5-5 mg/day; N = 72

**Notes about the interventions:**
Olanzapine
Flexible dose of 5, 10, 15 or 20mg/day

Risperidone
Flexible dose of 1.25, 2.5, 3.75 or 5Mg/day

All medication was dispensed in identical-looking capsules.

**Outcomes**

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Leaving the study early:** Leaving because of adverse effects

**Other:** Subjective experience, self-reported cannabis use, OCDUS, DDQ

**Quality**

**1.1 The study addresses an appropriate and clearly focused question.:** Adequately addressed

**1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately

**1.3 An adequate concealment method is used.:** Not addressed

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered

**1.5 The treatment and control groups are similar at the start of the trial.:** Not reported adequately

**1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Adequately addressed

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** 20-50%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Well covered

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not addressed

**2.1 How well was the study done to minimise bias?:** +

**References of included studies (update)**

**DEHAAN2003**

*de Haan, L.; Van Bruggen, M.; Lavalaye, J.; Booij, J.; Dingemans, P.M.; Linszen, D. (2003) Subjective experience and D2 receptor occupancy in patients with recent-onset schizophrenia treated with low-dose olanzapine or haloperidol: a randomized, double-blind study. *American Journal of Psychiatry* 160(**2**): 303 - 309.

**LEE2007**

*Lee ,S.M.; Chou,Y.H.; Li, M.H.; Wan, F.J.; Yen, M.H. (2007) Effects of antipsychotics on cognitive performance in drug-naive schizophrenic patients. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 31(**5**): 1101 - 1107.

**LIEBERMAN2003A**

*Lieberman,J.A.; Tollefson,G.; Tohen,M.; Green,A.I.; Gur,R.E.; Kahn,R.; McEvoy,J.; Perkins,D.; Sharma,T.; Zipursky,R.; Wei,H.; Hamer,R.M.; HGDH Study Group (2003) Comparative efficacy and safety of atypical and conventional antipsychotic drugs in first-episode psychosis: a randomized, double-blind trial of olanzapine versus haloperidol. *American Journal of Psychiatry.* 160(**8**): 1396 - 1404.

Lieberman,J.A.; Tollefson,G.; Tohen,M.; Green,A.I.; Gur,R.E.; Kahn,R.; McEvoy,J.; Perkins,D.; Sharma,T.; Zipursky,R.; Wei,H.; Hamer,R.M.; HGDH Study Group (2003) Comparative efficacy and safety of atypical and conventional antipsychotic drugs in first-episode psychosis: a randomized, double-blind trial of olanzapine versus haloperidol: Erratum. *American Journal of Psychiatry.* 160(**10**).

Green,A.I.; Lieberman,J.A.; Hamer,R.M.; Glick,I.D.; Gur,R.E.; Kahn,R.S.; McEvoy,J.P.; Perkins,D.O.; Rothschild,A.J.; Sharma,T.; Tohen,M.F.; Woolson,S.; Zipursky,R.B.; HGDH Study Group (2006) Olanzapine and haloperidol in first episode psychosis: two-year data. *Schizophrenia Research.* 86(**1-3**): 234 - 243.

Keefe,R.S.; Seidman,L.J.; Christensen,B.K.; Hamer,R.M.; Sharma,T.; Sitskoorn,M.M.; Lewine,R.R.; Yurgelun-Todd,D.A.; Gur,R.C.; Tohen,M.; Tollefson,G.D.; Sanger,T.M.; Lieberman,J.A. (2004) Comparative effect of atypical and conventional antipsychotic drugs on neurocognition in first-episode psychosis: a randomized, double-blind trial of olanzapine versus low doses of haloperidol. *American Journal of Psychiatry* 161(**6**): 985 - 995.

Keefe,R.S.; Seidman,L.J.; Christensen,B.K.; Hamer,R.M.; Sharma,T.; Sitskoorn,M.M.; Rock,S.L.; Woolson,S.; Tohen,M.; Tollefson,G.D.; Sanger,T.M.; Lieberman,J.A.; HGDH-Research-Group (2006) Long-term neurocognitive effects of olanzapine or low-dose haloperidol in first-episode psychosis. *Biological Psychiatry.* 59: 97 - 105.

Strakowski,S.M.; Johnson,J.L.; DelBello,M.P.; Hamer,R.M.; Green,A.I.; Tohen,M.; Lieberman,J.A.; Glick,I.; Patel,J.K.; HGDH Research Group (2005/10/15/) Quality of life during treatment with haloperidol or olanzapine in the year following a first psychotic episode.[see comment]. *Schizophrenia Research.* 78(**2-3**): 161 - 169.

Zipursky,R.B.; Christensen,B.K.; Daskalakis,Z.; Epstein,I.; Roy,P.; Furimsky,I.; Sanger,T.; Kapur,S. (2005) Treatment response to olanzapine and haloperidol and its association with dopamine D receptor occupancy in first-episode psychosis. *Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie.* 50: 462 - 469.

**MCEVOY07A**

*McEvoy,J.P.; Lieberman,J.A.; Perkins,D.O.; Hamer,R.M.; Gu,H.; Lazarus,A.; Sweitzer,D.; Olexy,C.; Weiden,P.; Strakowski,S.D. (2007) Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: a randomized, double-blind 52-week comparison. *American Journal of Psychiatry.* 164(**7**): 1050 - 1060.

Keefe,R.S.; Sweeney,J.A.; Gu,H.; Hamer,R.M.; Perkins,D.O.; McEvoy,J.P.; Lieberman,J.A. (2007) Effects of olanzapine, quetiapine, and risperidone on neurocognitive function in early psychosis: a randomized, double-blind 52-week comparison.[see comment]. *American Journal of Psychiatry.* 164(**7**): 1061 - 1071.

**MOLLER2008**

*Moller, H.J; et al. (2008) Short-term treatment with risperidone or haloperidol in first-episode. *International Journal of Neuropsychopharmacology* 9: 1-13.

**SCHOOLER2005**

*Schooler,N.; Rabinowitz,J.; Davidson,M.; Emsley,R.; Harvey,P.D.; Kopala,L.; McGorry,P.D.; Van,Hove,I; Eerdekens,M.; Swyzen,W.; De Smedt, G.; Early Psychosis Global Working Group (2005) Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial.[see comment]. *American Journal of Psychiatry.* 162(**5**): 947 - 953.

Emsley,R.; Rabinowitz,J.; Medori,R. (2006) Time course for antipsychotic treatment response in first-episode schizophrenia. *American Journal of Psychiatry.* 163: 743 - 745.

Emsley,R.; Rabinowitz,J.; Medori,R.; Early-Psychosis-Global-Working-Group (2007) Remission in early psychosis: Rates, predictors, and clinical and functional outcome correlates. *Schizophrenia Research* 89: 129 - 139.

Harvey,P.D.; Rabinowitz,J.; Eerdekens,M.; Davidson,M. (2005) Treatment of cognitive impairment in early psychosis: a comparison of risperidone and haloperidol in a large long-term trial. *American Journal of Psychiatry.* 162(**10**): 1888 - 1895.

**VANNIMWEGEN2008**

van Nimwegen LJ, de Haan L, van Beveren NJ, van der Helm M, van den Brink W, Linszen D. (2008). Effect of olanzapine and risperidone on subjective well-being and craving for cannabis in patients with schizophrenia or related disorders: a double-blind randomized controlled trial. *Canadian Journal of Psychiatry*, 53(6):400-5.

## Acute treatment with antipsychotic medication

**Characteristics of included studies (previous guideline)**

| Study | Methods | Participants | Interventions | Outcomes | Notes |
|---|---|---|---|---|---|
| **Arvanitis1997** (North America 013) | Allocation: randomised - no further details.<br>Blindness: double-blind - no further details.<br>Duration: 6 weeks (preceded by 7 days washout). | Diagnosis: schizophrenia (DSM-III-R).<br>Inclusion criteria: BPRS* >/= 27; CGI >/= 4.<br>N = 361.<br>Age: mean = 37 years.<br>Sex: M 274, F 87 | 1. Quetiapine: fixed dose 75 mg/day. n = 53.<br>2. Quetiapine: fixed dose 150 mg/day. n = 48.<br>3. Quetiapine: fixed dose 300 mg/day. n = 52.<br>4. Quetiapine: fixed dose 600 mg/day.n = 51.<br>5. Quetiapine: fixed dose 750 mg/day. n = 54.<br>6. Haloperidol: fixed dose 12 mg/day. n = 52.<br>7. Placebo: n = 51. | Global state (CGI).<br>Mental state - general (BPRS).<br>Mental state - specific: negative (Modified SANS)<br>Mental state - specific: positive (BPRS)<br>Side effects - extrapyramidal (AIMS, Modified Simpson-Angus).<br>Side effects – need for anticholinergic medication<br>Side effects - specific list.<br>Leaving the study early. | * 0-6 scoring system. |

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|---|---|---|---|---|---|
| **Barnas1987** | Allocation: random - no further information.<br>Blinding: double - used identical tablets.<br>Duration: 7 weeks (preceded by washout of 7 day for oral, 3 months for depots). | Diagnosis: schizophrenia (DSM-III-R).<br>N=30.<br>Age: mean ~34 years.<br>Sex: 20 M, 10 F.<br>History: duration ill 6 months - >5 years. | 1. Zotepine: mean dose ~ 94mg/day (SD~29). n =15.<br>2. Haloperidol: mean dose ~ 4mg/day (SD~1). n =15. | Leaving study early.<br>Global impression (CGI).<br>Mental state (BPRS, SANS [Munich version]).<br>Side effects (German version of the DOTES, Lab tests).<br><br>Unable to use -<br>ECG and EEG (no data). | Intention-to-treat analysis used last observation carried forward. |
| **Beasley1996a**<br><br>**(Tollefson 1998)** | Duration:<br>6 weeks<br>Washout:<br>4-7 days<br>Concomitant medications:<br>As required:<br>lorazepam and/or benztropine mesylate | Age: Mean (SD): 35 (8) - 37 (10) years<br>Sex: 78.3 - 92.3% M<br>Illness: schizophrenia<br><br>Diagnosis: DSM-III-R<br>N: 335<br>Duration of illness:<br>Not stated.<br>Special characteristics:<br>Subtype:<br>Paranoid: placebo 60.3%; OLZ-L 55.4%; OLZ-M 64.1%; OLZ-H 58.0%; HAL 59.4%<br>Disorganised: placebo 7.4%; OLZ-L 4.6%; OLZ-M 4.7%; OLZ-H 7.2%; HAL 5.8%<br>Undifferentiated: placebo 32.4%; OLZ-L 40.0%; OLZ-M 31.3%; OLZ-H 34.8%; HAL 34.8% | Intervention:<br>Olanzapine<br>N: 198<br>Dose:<br>OLZ-L: 2.5, 5, or 7.5 mg/day (n=65)<br>OLZ-M: 7.5, 10, or 12.5 mg/day (n=64)<br>OLZ-H:12.5, 15, or 17.5 mg/day (n=69)<br><br>Control:<br>Haloperidol<br>N: 69<br>Dose:<br>10, 15, or 20 mg/day | | Authors' conclusions:<br>Contributions from a more selective mesolimbic dopaminergic profile… may explain the differential benefit seen with olanzapine in the treatment of comorbid anxious and depressive symptoms in schizophrenia. |

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| | Comments:<br>Participants began therapy with the middle dose within their assigned dose range. On the basis of the investigator's clinical judgement, the dose could subsequently be decreased or increased to the optimal dosage in the permitted range. | Course:<br>Subchronic, acute exacerbation (AE): placebo 10.3%; OLZ-L 6.2%; OLZ-M 7.8%; OLZ-H 8.7%; HAL 8.7%<br>Chronic, AE: placebo 88.2%; OLZ-L 92.3%; OLZ-M 90.6%; OLZ-H 91.3%; HAL 91.3%<br>Unspecified: placebo 1.5%; OLZ-L 1.5%; OLZ-M 1.6%; OLZ-H 0.0%; HAL 0.0%<br><br>Inclusion/ exclusion criteria:<br>Minimum 18-item Brief Psychiatric Rating Scale (BPRS) total score of at least 24 and a Clinical Global Impression-Severity (CGI-S) of Illness score greater than or equal to 4. 18-65 years old.<br>Exclude: A diagnosis of a DSM-III-R organic mental disorder or substance-use disorder active within 3 months of study entry or a serious suicidal risk. Participants with serious and unstable medical conditions.<br><br>Further details:<br>Required to be hospitalised for at least 2 weeks at the beginning of the study. | Control 2:<br>Placebo<br>N: 68 | | |

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| **Beasley1997** | Allocation: randomised - blocks of 5.<br>Blindness: double - no further details.<br>Duration:6 weeks (preceded by placebo lead-in of 4-7 days: 46 week extension for responders).<br>Multicentre: 50 sites. | Diagnosis: schizophrenia (DSM-III-R).<br>Inclusion criteria: BPRS >23, CGI >3, off neuroleptics prior to entering study, lead-in period responders (BPRS total decreased by >24% / <24) excluded.<br>N=431.<br>Age:18-65.<br>Sex: 275 M, 156 F.<br>Inclusion criteria: minimum BPRS score of 24, CGI-S score >3.<br>Setting: initially all in hospital.* | 1. Olanzapine (OLZ-1): dose: 1mg/day. n=88.<br>2. Olanzapine (OLZ-L): dose: 2.5-7.5mg/day. n=87.<br>3. Olanzapine (OLZ-M): dose: 7.5-12.5mg/day. n=86.<br>4. Olanzapine (OLZ-H): dose 12.5-17.5mg/day**. n=89.<br>5. Haloperidol (HAL): dose 10-20mg/day. n=81.<br>Up to 10mg/day benzodiazepine allowed day 1-21 and biperiden up to 6mg/day allowed throughout. | Global state (CGI-S).<br>Mental state (BPRS***, PANSS).<br>Mental state (needing additional benzodiazepines).<br>Leaving study early.<br>Side effects (requiring benztropine).<br>Side effects (AIMS, Barnes Akathisia Scale, SAS).<br>Adverse events (COSTART list).<br><br>Unable to use -<br>Hospital status (no data).<br>Global state (PGI - no data).<br>Lab tests & physiological measures (no data). | *eligible for discharge if BPRS total decreased by >24% from baseline or was <24.<br><br>**Chosen as the comparator with other trials as mean dose = 13.2mg/day.<br><br>***BPRS (scored 0-6) extracted from PANSS - no reference given for validity of procedure.<br><br>***A priori efficacy >39 decrease from baseline or to <19 total. |

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|---|---|---|---|---|---|
| **Blin1996** | Allocation: randomised - no further description.<br>Blindness: double - medication in identical capsules.<br>Duration: 4 weeks. | Diagnosis: schizophrenia (DSM-III-R).<br>N=62.<br>Sex: 38 male, 24 female.<br>Age: mean 34.3, range 16-63.<br>History: acute exacerbation and psychotic anxiety; 9 ill < 1 year; 5 ill 1-3 years; 47 ill > 3 years.<br>Setting: hospital. | 1. Risperidone: dose mean 8.6mg/day, max = 12 mg/day. n=21.<br>2. Haloperidol: dose mean 9.2mg/day, max = 12 mg/day. n=20.<br>3. Methotrimeprazine: dose mean 125 mg/day, max = 125 mg/day. n=21.<br><br>Additional medication allowed: loprazolam (for sedation); biperiden (for EPS); heptaminal hydrochloride (for hypotension).<br>Individual dose titration in all groups. | Clinical improvement (20% reduction in PANSS score).<br>Global effect (GCI).<br>Mental state (BPRS, PANSS).<br>Psychotic Anxiety (PAS).<br>Side effects (Asberg Scale, ESRS).<br>Physiological monitoring (ECG, lab tests).<br>Leaving the study early. | Methotrimeprazine data not used in this review.<br><br>Intention to treat analysis undertaken. |

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| **Carriere2000** | Duration:<br>4 months<br>Washout:<br>None<br>Concomitant medications:<br>As required: anxiolytics, hypnotics, drugs to control incapacitating extrapyramidal symptoms, drugs for somatic disorders<br><br>Comments:<br>Initial dose was 20 mg/day haloperidol and 800 mg/day amisulpride; this could be adjusted thereafter according to participant's condition. | Age: Mean (SD): 30.9 (8.6)<br>Sex: 68% (n=136) M<br>Illness: combined diagnoses<br>Diagnosis: DSM-IV<br>N: 199<br>Inclusion/ exclusion criteria:<br>Participants of either sex, with paranoid schizophrenia or schizophreniform disorder.<br>Exclusion: Participants requiring mood regulators or antidepressants; concomitant serious diseases; alcohol or drug addiction; agitation due to organic, toxic or iatrogenic causes; or sensitivity to haloperidol or benzamides.<br>Further details:<br>Majority of participants (82%) were classified as schizophrenics of the paranoid type according to DSM-IV criteria and duration of illness; others suffered from schizophreniform disorders. | Intervention:<br>Amisulpride<br>N: 94<br>Dose:<br>400-1200 mg/day oral<br><br>Control:<br>Haloperidol<br>N: 105<br>Dose:<br>10-30 mg/day oral<br>Intervention group n:<br>24 (26%) participants withdrew, due to adverse events (n=4, 4%), uncooperativity (n=8, 9%), lack of efficacy (n=6, 6%), lost to follow-up (n=2, 2%), recovery (0) and other (n=4, 4%).<br><br>Control group n:<br>46 (44%) participants withdrew, due to adverse events (n=22, 21%), uncooperativity (n=9, 9%), lack of efficacy (n=9, 9%), lost to follow-up (n=3, 3%), recovery (n=1, 1%) and other (n=2, 2%). | Amisulpride (n=94): extrapyramidal disorder (n=22, 23%); depression (n=1, 1%); hypertonia (n=6, 6%); tremor (n=2, 2%); somnolence (n=1, 1%); dry mouth (n=1, 1%); hyperkinesia (n=2, 2%); weight increase (n=7, 7%).<br>Haloperidol (n=105): extrapyramidal disorder (n=49, 47%); depression (n=11, 10%); hypertonia (n=10, 10%); tremor (n=8, 8%); somnolence (n=6, 6%); dry mouth (n=6, 6%); dyskinesia (n=6, 6%); hyperkinesia (n=5, 5%); suicide attempt (n=5, 5%). | Authors' conclusions:<br>Amisulpride is globally superior to haloperidol in the treatment of acute exacerbations of schizophrenia and significantly improves participants' quality of life and social adjustment. |

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| **Ceskova1993** | Allocation: randomised.<br>Blindness: double - administered as monotherapy in oral solution.<br>Duration: 8 weeks. | Diagnosis: schizophrenia/schizoaffective disorder (ICD-9).<br>N=62.<br>Sex: 17 female, 45 male.<br>Age: mean 35.8 years.<br>Duration of illness: mean 10.4 years.<br>Setting: hospital. | 1. Risperidone: individual dose titration, mean 9.5mg/day, range 2-20 mg. n=31.<br>2. Haloperidol: individual dose titration, mean 9.9mg/day, range 2-20mg. n=31.<br><br>Additional medication allowed: antiparkinsonian (EPS); minor tranquillisers or promethazine (insomnia, akathisia); dihydroergotamine (dry mouth or vertigo). | Global effect (Serejskij's modified scale).<br>Mental state (BPRS).<br>Side effects (DVP scale, use of antiparkinsonian medication).<br>Leaving the study early. | Intention-to-treat analysis for side effects, unclear whether also done for efficacy analysis.<br><br>No standard deviations for continuous data, these data not used. |

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| **Cetin1999** | Duration:<br>6 weeks<br>Washout:<br>1 week (placebo)<br>Concomitant medications:<br>Medication to control EPS and lorazepam (for sedation) were allowed<br><br>Comments:<br>Purpose of study was to determine optimal dose of risperidone | Age: not stated<br>Sex: not stated<br>Illness: schizophrenia<br>Diagnosis: not stated<br>N: 70<br>Duration of illness:<br>not stated<br>Inclusion/ exclusion criteria:<br>not stated | Intervention:<br>risperidone<br>N: 50<br>Dose:<br>2mg/day (n=10);<br>4mg/day (n=10);<br>6mg/day (n=10);<br>8mg/day (n=10);<br>10mg/day (n=10)<br>oral<br><br>Control:<br>haloperidol<br>N: 20<br>Dose:<br>20mg/day<br>oral | The incidence of extrapyramidal side effects was significantly higher in participants treated with 8mg and 10mg of risperidone than in participants receiving 2, 4 and 6mg of risperidone. | Authors' conclusions:<br>The optimal daily dose of risperidone for most schizophrenia participants in this study population was 6mg. The present study replicates the findings of previous studies (specifically Chouinard 1993 and Marder 1994)<br><br>Comments:<br>Positive symptom scores were significantly lower after >=6mg doses of risperidone and 20mg haloperidol than 2 or 4mg risperidone.<br>Negative symptom scores were lower after >=6mg risperidone than haloperidol or 2 or 4mg risperidone. |

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| **Chouinard1993** | Allocation: randomised - no further description given.<br>Blindness: double - identical tablets.<br>Duration: 8 weeks (preceded by one week washout).<br>Multicentre. | Diagnosis: schizophrenia (DSM-III-R).<br>N=135.<br>Sex: male 96, female 39.<br>Age: mean 37 years, range 19-67.<br>History: duration of current hospitalisation - mean 2 years, range 0-23years; number of hospitalisations: mean 7, range 0-50. | 1. Risperidone: dose 2mg/day. n=24.<br>2. Risperidone: dose 6mg/day. n=22.<br>3. Risperidone: dose 10 mg/day. n=22.<br>4. Risperidone: dose 16mg/day. n=24.<br>5. Haloperidol: dose 20mg/day. n=21.<br>6. Placebo. n=22.<br>All fixed doses.<br>Additional medication allowed: chloral hydrate or benzodiazepine (sedation); procyclidine or biperidin (EPS). | Clinical improvement (20% reduction of total PANSS score).<br>Global effect (CGI).<br>Mental state (BPRS - PANSS derived, PANSS).<br>Side effects (ESRS, UKU, use of antiparkinsonian medication, use of sedative medication).<br>Physiological monitoring (ECG, vital signs, lab tests).<br>Leaving the study early. | Intention-to-treat analysis undertaken. |

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| **Claus1991** | Allocation: randomised - no further information given.<br>Blindness: double - matched oral solutions; investigators asked to guess double-blind code.<br>Duration: 12 weeks (preceded by placebo washout week).<br>Multicentre. | Diagnosis: schizophrenia with chronic course (DSM-III-R).<br>N=44.<br>Sex: male 28, female 14.<br>Age: mean 38.2 years, range 20-66 years.<br>History: duration of hospitalisation, < 10 years; age at onset of illness, mean 24.1 years, range 14-53 years.<br>Setting: hospital. | 1. Risperidone: dose mean 12mg/day. n=21.<br>2. Haloperidol: dose mean 10.3mg/day. n=21.<br>Individual dose titration for the first six weeks, fixed dose thereafter.<br>Additional medication allowed: diazepam (sedation); dexetimide (EPS); etybezatropine IM (acute dystonia). | Clinical improvement (20% reduction of total PANSS).<br>Global effect (CGI).<br>Mental state (PANSS, SADS-C).<br>Behaviour (NOSIE-30).<br>Individual target symptom (visual analogue scale).<br>Sleep quality (visual analogue scale).<br>Comparison with previous treatment (investigator and recipient).<br>Side effects (ESRS, symptom checklist).<br>Physiological monitoring (ECG, vital signs, weight, lab tests).<br>Leaving the study early. | Intention to treat analysis for side-effects, two participants excluded from efficacy analysis.<br><br>No standard deviations for continuous data, these data not used. |
| **Conley2001** | Duration:<br>8 weeks<br>Washout:<br>1 week gradual discontinuation<br>Concomitant medications:<br>Not stated | Age: mean R 41.0 (11.0) years, OLZ 38.9 (10.5)years<br>Sex: 274 M, 103 F<br>Illness: combined diagnoses<br>Diagnosis: DSM-IV<br>N: 377<br>Duration of illness:<br>mean R 16.5 (10.5)years, OLZ 15.4 (10.6) years | Intervention:<br>risperidone<br>N: 188<br>Dose:<br>2-6mg/day (flexible dose)<br>oral | Serious adverse event: R 15/188, OLZ 22/189<br>Psychosis: R 8/188, OLZ 8/189<br>Suicide attempt: R 2/188, OLZ 5/189<br>Agitation: R 3/188, OLZ 3/189<br>Depression: R 3/188, OLZ 3/189<br>Insomnia: R 3/188, OLZ 2/189 | Authors' conclusions:<br>Both risperidone and olanzapine were generally well tolerated and efficacious in the treatment of people with schizophrenia and schizoaffective disorder. |

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| | Comments:<br>Both drugs given once daily according to following regimes: days 1-2, 2mg R or 10mg OLZ; days 3-7, 2-4mg R or 5-10mg OLZ; days 8-14, 2-6mg R or 5-15mg OLZ; days 15-56, 2-6mg R or 5-20mg OLZ | Special characteristics:<br>schizophrenia (n=325) or schizoaffective disorder (n=52)<br>Inclusion/ exclusion criteria:<br>Baseline PANSS score of 60-120, aged 18-64 years. Out-patients or in-patients hospitalised <=4weeks.<br>Exclusion criteria: another axis I diagnosis, substance abuse in 3 months before trial, CNS disease, use of concomitant mood stabilisers or antidepressants, history of clozapine treatment for >4weeks, being known by the investigator to be sensitive or unresponsive to risperidone or olanzapine<br>Further details:<br>79% were out-patients | Control:<br>olanzapine<br>N: 189<br>Dose:<br>5-20mg/day<br>oral<br><br>Intervention group n: 53/188 (adverse event 22/188)<br><br>Control group n: 43/189 (adverse event 17/189) | Hallucinations: R 2, OLZ 3<br>Drug abuse: R 0, OLZ 3<br>Cardiovascular symptoms: R 0, OLZ 3<br>Gastrointestinal disorders: R 0, OLZ 3<br>Other: R 14, OLZ 21<br><br>Weight gain: R 3.4lb (SD 7.8), OLZ 7.2lb (SD 11.2)<br>Increase in body weight of >=7%: R 18/155, OLZ 44/161<br><br>Less serious AEs:<br>Somnolence: R 69/188, OLZ 73/189<br>Insomnia: R 45, OLZ 35<br>Headache: R 41, OLZ 32<br>Agitation: R 29, OLZ 40<br>Dry mouth: R 21, OLZ 42<br>Rhinitis: R 30, OLZ 31<br>Dizziness R 26, OLZ 27<br>Anxiety: R 20, OLZ 23<br>Vision abnormalities: R 12, OLZ 19<br><br>Extrapyramidal symptoms: R 45/188, OLZ 38/189<br>Participants using antiparkinsonian medication: R 61/188, OLZ 53/189. | The frequency and severity of extrapyramidal symptoms were similar in the two treatment groups. PANSS scores on two factors - positive symptoms and anxiety/ depression - were better with risperidone than with olanzapine among participants who completed the 8-week trial. Olanzapine treatment was associated with a magnitude of weight gain that may constitute a meaningful health hazard. |

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| **Cooper1999a** | Allocation: blocks of 6 randomisation undertaken by drug company. Code held by drug company.<br>Blinding: double, identical tablets. Double dummy technique used.<br>Duration: 8 weeks, preceded by 1 dosing interval for participants on depot.<br>Inclusion criteria: baseline CGI score of 4.<br>Exclusion: physical ill health, substance abuse.<br>Intention to treat analysis: last observation carried forward.<br>Power calculation to detect a change of 8.8 from baseline in BPRS total score. | Diagnosis: schizophrenia, acute exacerbation (DSM-III-R).<br>N=159.<br>Age: 18-65, (mean age; zotepine group 39.6 years; chlorpromazine 41.0 years; placebo 36.3years)<br>Sex: 115 M, 44 F.<br>History: mostly in-patients, duration of illness, range 6-440 months.<br>Multicentre. | 1. Zotepine: dose titrated from 150mg day to 300mg day over first 7 days, n=53.<br>2. Chlorpromazine: dose titrated from 200mg a day to 600mg a day over first 7 days, n=53.<br>3.Placebo. n=53.<br>Benzodiazepines or chloral hydrate allowed. All other treatments permitted, including anticholinergic medication. Allowed to drop down to lower doses if intolerant to higher dose.<br>Withdrawn from study if intolerant of lower dose. | Leaving the study early.<br>Global impression (CGI - no data).<br>Mental state (BPRS, SANS).<br>Side effects (AIMS, SAS, adverse events using COSTART terms - only reported side-effects if they were reported 5 or more times)<br>Weight.<br>Pulse.<br>Unable to use Benzodiazepine use (No data).<br>BP (no SD).<br>Discharge from inpatient status. | |

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| **Delcker1990** | *Allocation:*<br>Random – no further details.<br><br>*Blinding:*<br>Double – no further details.<br><br>*Setting:*<br>Single centre (Zwiefalten Psychiatric Hospital). In-patients.<br><br>*Duration:*<br>6 weeks, preceded by a washout period of 4 – 28 days (mean = 8.7 days). | Diagnosis:<br>Schizophrenia (ICD-9), paranoid (n = 24), residual (n = 16) and hebephrenic (n = 1).<br><br>Age:<br>Amisulpride group: mean = 43.3 yrs.<br>Haloperidol group: mean = 40.1 yrs.<br><br>Sex: 33 M, 8 F<br><br>N: 41<br><br>History:<br>Mean duration of illness 14.3 – 17.3 years (range 0.3 – 36 years). | 1. amisulpride: dose 490-1000 mg/day (mostly 500-700 mg/day). n = 21.<br><br>2. haloperidol: dose 5-40 mg/day (mostly 20-25 mg/day). n = 20. | Leaving the study early.<br><br>Extrapyramidal side effects:<br>Use of biperiden<br>Documented EPS/ scores<br><br>Other adverse effects:<br>Use of sedatives (diazepam)<br>Use of flunitrazepam.<br><br>Unable to use:<br>Global state:<br>CGI (can't use – graph)<br>Mental state:<br>BPRS (can't use – graph)<br>AMDP (can't use – graph)<br><br>Side effects:<br>Simpson (can't use – graph)<br>Webster (can't use – graph) | |

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| **Dieterle1999** | Allocation: random - no further information.<br>Blinding: double - used capsules of identical appearance.<br>Duration: 28 days (preceded by washout of 3-5 days for oral, 14 days for depots).<br>Single centre | Diagnosis: schizophrenia (ICD 9).<br>N=40.<br>Age: mean ~zotepine group 31.1 years; perazine 35.8 years.<br>Sex: 13 M, 27F.<br>History: inpatients, chronic diagnosis. | 1. Zotepine: mean dose - 241mg/day (SD~70). n=20.<br>2. Perazine: mean dose - 348mg/day (SD~98). n=20. | Leaving study early.<br><br>Unable to use<br>Global impression (CGI - no mean or SD).<br>Mental state (BPRS, SANS).<br>Side effects (Webster and SAS, AMDP Lab tests).<br>EEG<br>ECG | |
| **Fleischhacker1989** | Allocation: random - no further details.<br>Blinding: double - used identical tablets.<br>Duration: 6 weeks. | Diagnosis: schizophrenia (DSM-III).<br>N=40.<br>Age: mean ~ 33 years.<br>Sex: 29 M, 11 F.<br>History: ill 3 months to > 5 years. | 1. Zotepine: mean dose 309mg/day. n=20.<br>2. Haloperidol: mean dose 14.5mg/day. n=20. | Side effects (Lab tests).<br><br>Unable to use -<br>Global effect (CGI - no usable data).<br>Mental State (BPRS - no SD).<br>Side effects (DOTES - no mean or SD).<br>ECG (not reported). | |
| **Fleischhacker1996** (Multi-country 014) | Allocation: randomised, no further details.<br>Blindness: double-blind, no further details.<br>Duration: 6 weeks (preceding by 2 days washout). | Diagnosis: schizophrenia (DSM-III-R).<br>Inclusion criteria: PANSS >/= 60, CGI >/= 4.<br>N = 448.<br>Age: mean = 37 years.<br>Sex: M 305, F 143. | 1. Quetiapine: mean dose 455 mg/day (50-800 mg/day), n = 221.<br>2. Haloperidol: mean dose 8 mg/day (1-16 mg/day), N 227. | Global state (CGI).<br>Mental state - general (PANSS).<br>Leaving the study early.<br>Side effects - extrapyramidal (AIMS, Simpson Angus Scale).<br>Side effects – need for anticholinergic medication | |

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| **Fleurot1997** | *Allocation:*<br>Random – no further details.<br><br>*Blinding:*<br>Double – no further details.<br><br>*Duration:*<br>8 weeks, preceded by a 3 to 6 day washout period.<br><br>*Setting:*<br>Multicentre, in-patients. | *Diagnosis:*<br>Schizophrenia (DSM IV)<br><br>*Age:* mean 36.5 years<br><br>*Sex:* Not stated.<br><br>*N:* 228<br><br>*History:* Currently acutely ill. Mean duration of illness 9.0 years. | amisulpride 800 mg/day.<br><br>risperidone 8 mg/day. | Leaving the study early.<br>Global state: response (CGI)<br>Mental state: BPRS total. PANSS positive change scores.<br><br>Weight gain. | |
| **Gureje1998** | Allocation: randomised, computer-generated, blocks for each investigator, 1:1, concealed from investigator.<br>Blindness: double, medication kits issued.<br>Duration: 30 weeks. | Diagnosis: schizophrenia, schizophreniform and schizoaffective disorder (DSM-IV).<br>N=65.<br>Age: not stated.<br>Sex: not stated.<br>Setting: not stated, multicentre, Australia & New Zealand. | 1. Olanzapine: dose 10-20mg/day. n=32.<br>2. Risperidone: dose 4-8mg/day. n=33. | Leaving study early.<br>Global state: CGI-S.<br>Mental state: BPRS, PANSS.<br>Other adverse events: COSTART list, weight change.<br>Quality of life: QLS.<br><br>Unable to use -<br>Quality of life: SF-36 (no total score). | |

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| **Hale2000** | **Duration:**<br>8 weeks<br>**Washout:**<br>3-7 days<br>**Concomitant medications:**<br>Not stated | **Age:** Mean: 35.04 (range 17-66) years<br>**Sex:** 400/595 M<br>**Illness:** schizophrenia<br>**Diagnosis:** DSM-III-R<br>**N:** 617<br>**Duration of illness:**<br>Not stated<br>**Special characteristics:**<br>Disorganised 82/595; Catatonic 9/595; Paranoid 305/595; Residual 52/595; Unspecified 173/595<br>**Inclusion/ exclusion criteria:**<br>Aged 18-65 years; required hospitalisation; score >2 for at least two of the following PANSS items (sum of scores >=8): conceptual disorganisation, hallucinatory behaviour, suspiciousness, unusual thought content; <3 for all items on Simpson-Angus scale and AIMS.<br>Exclude: Non-responders to any antipsychotic agent within the past 5 years; unrateable using the battery of psychiatric and movement rating scales; current primary psychiatric diagnosis other than schizophrenia; confounding medical or neurological disorders; history of substance abuse; clinically relevant electrocardiogram (ECG) abnormalities; decrease in PANSS score >=20 over a 7-day placebo run. | **Intervention:**<br>Sertindole<br>**N:** 492<br>**Dose:**<br>8 mg/day (n=120); 16 mg/day (n=127);20 mg/day (n=128); 24 mg/day (n=117)<br>oral<br><br>**Control:**<br>Haloperidol<br>**N:** 125<br>**Dose:**<br>10 mg/day<br>oral | | 22 participants missing from the ITT analysis.<br><br>During the active treatment phase, participants in the sertindole groups initially received sertindole 4mg/day for 3 days. Dose was then increased every 3 days by 4 mg until appropriate dose (8, 16, 20 mg/day) was reached.<br>Participants in the haloperidol group received haloperidol 5mg for 3 days, then on day 4 dose was increased to 10 mg.<br><br>Participants were administered matching placebo in addition to their randomised treatment, all participants took 3x tablets and 2x capsules every day. |

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| **HGBL1997**<br>Eli Lilly. Data on file. Data supplied to the Cochrane Schizophrenia Group 1999. | Allocation: randomised, computer-generated, blocks, 1:1 for each investigator, concealed from investigators.<br>Blindness: double, medication kits issued.<br>Duration: 4 weeks (preceded by placebo lead-in of 4-7 days. | Diagnosis: schizophrenia (DSM-IV).<br>N=33.<br>Age: not stated.<br>Sex: not stated.<br>Setting: in-patients. | 1. Olanzapine: dose 5-20mg/day. n=15.<br>2. Flupentixol: dose 5-20mg/day. n=13. | Leaving study early.<br>Other adverse events: COSTART list, weight change.<br><br>Unable to use -<br>Global state: (no data).<br>Mental state: (no data).<br>Side effects: extrapyramidal (no data). | |
| **HGCJ(Hong Kong)1999** | Allocation: randomised, computer-generated, blocks, 1:1 for each investigator, concealed from investigators.<br>Blindness: double, medication kits issued.<br>Duration: 14 weeks. | Diagnosis: schizophrenia, schizophreniform disorder, schizoaffective disorder (DSM-IV).<br>N=31.<br>Age: not stated.<br>Sex: not stated.<br>Setting: in-patients and out-patients. | 1. Olanzapine: dose 5-20mg/day. n=17.<br>2. Haloperidol: dose 5-20mg/day. n=14. | Leaving study early.<br>Global state: CGI-S.<br>Mental state: BPRS, MADRS, PANSS.<br>Other adverse events: COSTART list, weight change.<br><br>Unable to use -<br>Side effects: extrapyramidal (no data). | |

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| **HGCU(Taiwan) 1998** | Allocation: randomised, blocks, computer-generated, 1:1 for each investigator, concealed from investigators.<br>Blindness: double, medication kits issued.<br>Duration: 14 weeks. | Diagnosis: schizophrenia, schizophreniform disorder, schizoaffective disorder (DSM-IV).<br>N=54.<br>Age: not stated.<br>Sex: not stated.<br>Setting: not stated. | 1. Olanzapine: dose 5-20mg/day. n=26.<br>2. Haloperidol: dose 5-20mg/day. n=28. | Leaving study early.<br>Global state: CGI-S.<br>Mental state: BPRS, MADRS, PANSS.<br>Other adverse events: COSTART list, weight change.<br><br>Unable to use -<br>Side effects: extrapyramidal (no data). | |
| **Hillert1994** | *Allocation:*<br>Random – no further details.<br><br>*Blinding:*<br>Double – no further details.<br><br>*Duration:*<br>6 weeks, preceded by a washout period of 1-9 days.<br><br>*Setting:*<br>Multi-centre (11 German centres), in-patients. | *Diagnosis:*<br>Schizophrenia (DSM-III-R), paranoid or undifferentiated type.<br><br>*Age:* range 18 – 65 years.<br><br>*Sex:* 74 M, 58 F<br><br>*N:* 132<br><br>*History:*<br>Currently acute with predominant positive symptomatology. Duration of illness not described. BPRS score of 36 or higher. SANS score less than 55. | 1. amisulpride: dose 1000mg/day fixed dose, could be adjusted to minimum dose of 600 mg/day (mean dose 956 mg/day). n = 70.<br><br>2. flupentixol: dose 25mg/day fixed dose, could be adjusted to minimum dose of 15 mg/day (mean dose 22.6 mg/day). n = 62. | Leaving the study early.<br><br>Global state:<br>Reduction in dose due to improvement; response (CGI), CGI-S, GAS.<br>Mental state:<br>Response (BPRS); BPRS total and subscores, SAPS, SANS.<br><br>Extrapyramidal side effects:<br>Documented EPS/ scores<br>SAS<br>BAS<br>AIMS<br><br>Weight gain<br>Prolactin levels | |

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| **Hoyberg1993** | Allocation: randomised - no further description.<br>Blindness: double - identical appearance.<br>Duration: 8 weeks.<br>Multicentre, multinational. | Diagnosis: schizophrenia (DSM-III-R).<br>N=107.<br>Sex: male 77, female 30.<br>Age: mean 36 yrs, range 20-67.<br>History: chronic. | 1. Risperidone: dose 5-15mg/day, mean 8.5 mg/day. n=55.<br>2. Perphenazine: dose 16mg-48mg/day, mean 28mg/day. n=52.<br>Individual dose titration for 4 weeks fixed dose thereafter. | Clinical improvement (>20% reduction in total PANSS or BPRS score, CGI improvement).<br>Severity of illness (CGI severity).<br>Mental state (PANSS, BPRS - PANSS derived).<br>Side effects (ESRS, UKU, use of antiparkinsonian medication).<br>Physiological monitoring (lab tests).<br>Leaving the study early. | |
| **Huttunen1995** | Allocation: randomised - no further information.<br>Blindness: double - no further information.<br>Duration: 6 weeks.<br>Multicentre. | Diagnosis: schizophrenia (DSM-III-R).<br>N=98.<br>Sex: 47 male, 51 female.<br>Age: mean 36 yrs, range 11-43.<br>History: chronic, but acutely ill, mean age at onset 23.5 yrs, range 11-43. | 1. Risperidone: dose mean 8mg/day, range 2-20mg/day. n=48.<br>2. Zuclopenthixol: dose mean 38mg/day, range 10-100mg/day. n=50.<br>Individual dose titration in both groups. | Global effect (CGI).<br>Mental state (PANSS, BPRS - PANSS derived).<br>Comparison with previous medication (categorical scale).<br>Side effects (ESRS, UKU, numbers requiring antiparkinson medication, investigator & recipient impression of interference to daily life caused by adverse events).<br>Physiological monitoring (vital signs, ECG, lab tests).<br>Leaving the study early. | |

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| **Jakovljevic1999** (now published as Dossenbach *et al.*, 2004) | Allocation: randomised, blocks 1:1, computer-generated, concealed from investigators.<br>Blindness: double, medication kit issued.<br>Duration: 6 weeks followed by extension for 22 weeks (preceded by washout period of 2-9 days). | Diagnosis: schizophrenia, (DSM-IV).<br>Inclusion criteria: Aged 18-65 years, BPRS ≥42<br>& CGI-S ≥4.<br>N=60.<br>Setting: inpatient, 3 sites, Croatia. | 1. Olanzapine: dose 5-20mg/day. n=30.<br>2. Fluphenazine: dose 6-21mg/day. n=30. | 22 week data: Leaving study early.<br>Global state: CGI-S.<br>Mental state: BPRS, PANSS.<br>Other adverse events: COSTART list, weight change.<br>Quality of life: Van Putten Scale, Drug Attitude Inventory, Leeds Sleep Evaluation Questionnaire.<br><br>Unable to use -<br>Side effects: extrapyramidal (no data). | |

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| **Janicak1999** (now published as Janicak *et al*., 2001) | Duration:<br>6 weeks<br>Washout:<br>not stated<br>Concomitant medications:<br>not stated | Age: not stated<br>Sex: not stated<br>Illness: schizoaffective disorder<br>Diagnosis: DSM-IV<br>N: 60<br>Duration of illness:<br>not stated<br>Inclusion/ exclusion criteria: 18 years or older<br>& have a minimum total baseline PANSS = 50.<br>Those with the bipolar subtype, manic phase, had a CARS-M total score of > 16, and those with the depressive subtype had a total HAM-D-24 score of >22 at entrance into the study.<br>Further details:<br>There were no differences between groups on such variables as age, sex, duration or severity of psychotic symptoms. | Intervention:<br>risperidone<br>N: not stated<br>Dose:<br>up to 10mg/day<br>oral<br><br>Control:<br>haloperidol<br>N: not stated<br>Dose:<br>up to 20mg/day<br>oral<br><br>5 in the haloperidol group withdrew due to adverse events compared to 0 in the risperidone group. | Based on Simpson-Angus scores haloperidol produced significantly more extrapyramidal symptoms than risperidone ($p<0.04$).<br>More participants on haloperidol dropped out because of side effects. | |

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| **Klieser1996** | Allocation: random, no further details.<br>Blinding: double, no further details.<br>Duration: four weeks. | Diagnosis: schizophrenia (ICD 9), acute, paranoid hallucinatory psychoses.<br>N=180.<br>Age: zotepine group, mean 32.5 years; risperidone 8mg group, mean 33.1 years; haloperidol group, 33.1 years.<br>Sex: 84 M, 96 F.<br>Duration of illness: zotepine group mean 2.3 years (1.3); haloperidol group mean 4.6 (4.1); risperidone 8mg group mean 4.3 (5.8). | 1. Zotepine: 3x75mg/day.<br>2. Risperidone: increased to 4mg/day over first 7 days (not included).<br>3. Risperidone: increased to 8mg/day over first 7 days.<br>4. Clozapine: increased to 400mg/day over first 7 days (not included).<br>5. Remoxipride: increased to 400mg/day over first 7 days (not use).<br>6. Haloperidol: 15mg/day.<br>7. Biperiden for side effects, diazepam and chloral hydrate allowed. | Global impression (CGI).<br>Mental state (BPRS,).<br>Side effects (SAS, Lab tests).<br>Cognition (SKT).<br>Unable to use -<br>ECG and EEG (no data).<br>Side effects (Lab tests - no data). | |
| **KnollCTR (Study ZT4002)** | Duration: 6 months<br>Washout: 2 weeks if MAOIs or fluoxetine had been taken. | Age: zotepine 33.5 years; haloperidol 34.8 years<br>Sex: 94/125 M<br>Illness: schizophrenia<br>Diagnosis: DSM-III-R<br>N: 125 | Intervention: Zotepine<br>N: 59<br>Dose: Days 1 and 2 150mg/day; days 3 and 4 200mg/day; from day 5 onwards 300mg/day. | Zotepine group: 55/59 participants reported a total of 166 AEs. The most common AEs were (no of participants):<br>Aesthenia (6)<br>Constipation (7) | |

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| | Concomitant medications: No other antipsychotic medication was permitted except for benzodiazepines and anticholinergic drugs to control significant EPS.<br>Comments: The mean treatment duration for zotepine was 102.7 days and for haloperidol was 101.5 days. 27 participants in the zotepine group changed from 300mg/day to 150 mg/day and 29 participant in the haloperidol group changed from 20mg/day to 10mg/day. | Duration of illness: not stated<br>Inclusion/ exclusion criteria: Disease had to be assessed as at least III on CGI scale. Participants were either not previously treated with a neuroleptic or required a change due to lack of efficacy or poor tolerability.<br>Exclusion criteria: hypersensitivity to neuroleptics; resistance to haloperidol; taken haloperidol in the previous 3 months; hospitalised for 3 months or more; patent neurological disease; participants with significant medical disorder; prolactin-related disorder; at risk of pregnancy; resistant schizophrenia; participants at risk of suicide; history of alcoholism or drug abuse. | If the participant experienced adverse events the dosage could be reduced to 150mg/day oral<br>Control: Haloperidol<br>N: 66<br>Dose: Days 1 and 2 6mg/day; days 3 and 4 10mg/day. Days 5 onwards 20mg/day. If the participant experienced adverse events the dosage could be reduced to 10mg/day oral<br>Intervention group n: number of dropouts = 36, AE 20, Lack of efficacy 10, stopped follow-up 1, Protocol violation 0, Other 5<br>Control group n: number of dropouts = 41, AE 17, Lack of efficacy 8, Stopped follow-up 2, Protocol violation 1, Other 13 | Anxiety (8) Dry mouth (7) Dyskinesia (5) EPS (3) Insomnia (10) Drowsiness (12) Trembling (5) Weight gain (4); mean weight gain 2.5kg<br>21 participants stopped treatment due to AEs. 13 participants reported at least one serious AE - mainly related to relapse.<br>Haloperidol group: 57/66 participants reported a total of 140 AEs. The most common AEs were (no of participants): Aesthenia (4) Constipation (6) Anxiety (14) Dry mouth (3) Dyskinesia (7) EPS (12) Insomnia (15) Drowsiness (7) Trembling (12) Weight gain (0) mean weight loss 0.5kg (p=0.003)<br>22 participants stopped treatment due to AEs. 18 participants reported at least one serious AE - mainly related to psychiatric admissions to hospital. | |

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| **Lecrubier2000** (now published as Sechter 2002) | Duration:<br>6 months (possible extension to 12 months) | Age: Mean: 38.4 years<br>Sex: 55% M (171/310)<br>Illness: schizophrenia<br>Diagnosis: DSM-IV<br>N: 310<br>Duration of illness:<br>Mean: 11.8 years<br>Special characteristics:<br>Mainly paranoid type: 73% (226/310)<br>Inclusion/ exclusion criteria:<br>Not stated | Intervention:<br>Amisulpride<br>N: 152<br>Dose:<br>Initial 600 mg/day, adj. 400-1000 mg/day<br><br>Control:<br>Risperidone<br>N: 158<br>Dose:<br>Initial 6 mg/day, adj. 4-10 mg/day | Both treatments did not provoke increase in extrapyramidal symptoms as measured by the Simpson-Angus, Barnes and Abnormal Involuntary Movement Scales. | |
| **Link1994** (Europe-Africa 007) | Allocation: randomised, no further details.<br>Blindness: double-blind, no further details.<br>Duration: 6 weeks (preceding by 1 day washout). | Diagnosis: schizophrenia (DSM-III-R).<br>Inclusion criteria: BPRS >/= 27, CGI >/= 4.<br>N = 201.<br>Age: mean ~ 33 years.<br>Sex: M 129, F 72. | 1. Quetiapine: mean dose 407 mg/day. n=101.<br>2. Chlorpromazine: mean dose 384 mg/day. n=100. | Global state (CGI).<br>Mental state - general (BPRS).<br>Mental state - specific: negative (PANSS, N)<br>Side effects - extrapyramidal (AIMS, Barnes akathisia Scale, Simpson-Angus).<br>Side effects - specific list.<br>Leaving the study early. | |

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| **Liu2000** | Duration:<br>12 weeks<br>Washout:<br>1 week | Age: Mean (SD): 33.9 (10.8) years<br>Sex: 40% male (n=15)<br>Illness: schizophrenia<br>Diagnosis: DSM-III-R<br>N: 38<br>Duration of illness:<br>Mean (SD): 7.8 (6.8) years<br>Inclusion/ exclusion criteria:<br>Total score > 65 on the Positive and Negative Syndrome Scale (PANSS). Patients with a previous history of physical illness or substance abuse that cast the diagnoses in doubt were excluded. | Intervention:<br>Risperidone<br>N: 19<br>Dose: not stated<br><br>Control:<br>Haloperidol<br>N: 19<br>Dose:<br>Not stated<br><br>Intervention group n:<br>7 dropped out of the trial; 2 did not complete the Continuous Performance Test (CPT) at the end of study.<br><br>Control group:<br>9 dropped out of the trial. | Not reported | |

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| **Loza1999** | Allocation: randomised, computer-generated, blocks for each investigator, 2:1, olanzapine to chlorpromazine, concealed from investigators.<br>Blindness: double, medication kits issued.<br>Duration: 6 weeks (preceded by washout phase of 2-9 days; extension for responders).<br>Multicentre: 2 sites, Egypt. | Diagnosis: schizophrenia (DSM-IV).<br>N=41.<br>Age: mean ~32 years.<br>Sex: ~ 80% M.<br>Setting: in-patients & out-patients. | 1. Olanzapine: dose 5-20mg/day. n=27.<br>2. Chlorpromazine: dose 200-800mg/day. n=14. | Leaving study early.<br>Other adverse events: COSTART list, weight change.<br><br>Unable to use -<br>Global state: CGI-S (no data).<br>Mental state: BPRS, PANSS (no useable data).<br>Side effects: extrapyramidal - UKU (no data).<br>Hospital status: (no data).<br>Laboratory tests & physiological measures: (no data). | |

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| **Malyarov1999** | Duration:<br>6 months<br><br>Comments: | Age: Average age: 24.5 years<br>Sex: 28/43 M<br>Illness: schizophrenia<br>Diagnosis: ICD10<br>N: 43<br>Duration of illness:<br><3 years<br>Special characteristics:<br>Patients with a diagnosis of schizophrenia with acute psychotic states. Hospitalised.<br>Inclusion/ exclusion criteria: not stated | Intervention:<br>Olanzapine<br>N: 15<br>Dose:<br>5-15 mg/day<br><br>Intervention 2:<br>Risperidone<br>N: 10<br>Dose: 3-6 mg/day<br><br>Control:<br>Haloperidol<br>N: 18<br>Dose:<br>5-20 mg/day<br><br>Intervention group:<br>0 dropouts<br><br>Intervention 2 group:<br>2 dropouts<br><br>Control group:<br>3 dropouts | Not reported. | |

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| **Marder1994** | Allocation: randomised - in blocks of 12.<br>Blindness: double - no further description.<br>Duration: 8 weeks (preceded by 1 week washout). | Diagnosis: schizophrenia (DSM-III-R); PANSS score 60-120.<br>N=388.<br>Age: mean 37.4 years, range 18-65.<br>Sex: Female 48, Male 340.<br>History: duration of illness, mean 15.7 years; duration of current hospitalisation, mean 29 weeks; number of previous hospitalisations, mean 9.1, range 0-61.<br>Setting: hospital. | 1. Risperidone: dose 2mg/day. n=63.<br>2. Risperidone: dose 6mg/day. n=64.<br>3. Risperidone: dose 10mg/day. n=65.<br>4. Risperidone: dose 16mg/day. n=64.<br>5. Haloperidol: dose 20mg/day. n=66.<br>6. Placebo: n=66.<br>Dose titrated, week 1 to a fixed maintenance dose.<br>Additional medication allowed: chloral hydrate / lorazepam (for sedation), medication to control EPS. | Clinical improvement (20% reduction in total PANSS, 20% reduction in BPRS, 20% reduction in BPRS and either posttreatment CGI 3 or less or BPRS total score 35 or less).<br>Time to clinical improvement.<br>Global effect (CGI).<br>Mental state (BPRS, PANSS).<br>Side effects (ESRS, modified UKU, spontaneous reports of adverse events).<br>Physiological monitoring (ECG, lab tests).<br>Leaving the study early. | |
| **Mesotten1991** | Allocation: randomised - no further description.<br>Blindness: double - identical medication.<br>Duration: 8 weeks (preceded by 1 week).<br>Multicentre. | Diagnosis: schizophrenia (N=46), schizophreniform disorder (N=2), schizoaffective disorder (N=6), paranoid disorder (N=4), other psychotic disorders (N=2) (DSM-III criteria).<br>N=60.<br>Age: mean 39.5 years, range 20-65.<br>Sex: male 37, female 23.<br>History: number of years since first hospitalisation: mean 5.7 years, range 0-38. | 1. Risperidone: dose mean 9.1mg/day. n=28.<br>2. Haloperidol: dose mean 9.4mg/day. n=32.<br>Individual dose titration week 1-4, fixed dose thereafter. | Global effect (CGI, subjective comparison with previous neuroleptic - investigator & recipient).<br>Mental state (BPRS).<br>Behaviour (NOISE).<br>Side effects (ESRS, use of medication for EPS, specific adverse experiences).<br>Physiological monitoring (ECG, vital signs, lab tests).<br>Leaving the study early. | |

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| **Min1993** | Allocation: randomised - sealed envelopes, no description of how code generated.<br>Blindness: double - identical medication.<br>Duration: 8 weeks (preceded by 1 week washout). | Diagnosis: schizophrenia (DSM-III-R), PANSS score >60<120.<br>N=35.<br>Age: mean 34.1years, range 18-59.<br>Sex: male 17, female 18.<br>History: number of previous hospitalisations, mean 3.1, range 15-41; duration of current hospitalisation, mean 154 days, range 1-554; age at onset of illness, mean 23.5 years, range 14-40. | 1. Risperidone: dose 5mg/day (n=8), 10mg/day (n=8).<br>2. Haloperidol: dose 5mg/day (n=4), 10 mg/day (n=15).<br>Week 1-2 dose was 5mg/day, if insufficient response dose increased to 10mg/day.<br>Additional medication allowed: lorazepam / oxazepam (sedation); benztropine mesylate (EPS). | Clinical improvement (20% reduction in PANSS score).<br>Global effect (GCI).<br>Mental state (BPRS - PANSS derived, PANSS).<br>Side effects (ESRS; modified UKU).<br>Physiological monitoring (ECG, lab tests, vital signs).<br>Leaving the study early.<br>Satisfaction with treatment (seven point scale). | |
| **Moller1997** | *Allocation:*<br>Random – no further details<br><br>*Blinding:*<br>Double – no further details<br><br>*Duration:*<br>6 weeks, preceded by a washout period of 1 week (or 1 day if | *Diagnosis:*<br>Schizophrenia (DSM-III-R), paranoid (37%), disorganised (38%) or undifferentiated (25%) type.<br><br>*Age:* mean 36 years.<br><br>*Sex:* 119 M, 72 F<br><br>*N:* 191 | 1. amisulpride: dose 800mg/day b.d., reduced to 600mg/day if needed. n = 95.<br><br>2. haloperidol: dose 20mg/day b.d., reduced to 15 mg/day if needed. n = 96. | Death (suicide).<br>Leaving the study early.<br><br>Global state:<br>CGI (response = item 2 or 1); reduced dose.<br>Mental state:<br>Improvement (BPRS, positive and negative PANSS); positive PANSS; negative PANSS; BPRS total and subscores; psychiatric adverse events. | |

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| | participants required immediate treatment).<br><br>*Setting:*<br>Multicentre (31 European centres in six countries between March 1993 and March 1995). Inpatients | *History:*<br>Currently acute exacerbation of chronic or subchronic illness. Score of 12 of more on the four core BPRS productive symptoms. Not treatment-resistant.<br>First episode service users with at least 6 months duration of illness could also be recruited. Mean duration of illness 10 years. | | Extrapyramidal side effects:<br>Use of antiparkinsonian medication<br>Documented EPS/ scores<br>SAS<br>BAS<br>AIMS | |
| **Muller-Siecheneder1998** | Duration:<br>6 weeks<br>Washout:<br>3 days<br>Concomitant medications:<br>As required: anticholinergic (biperiden) for acute dystonia and other EPS; diazepam up to 30mg/day | Age: 19-63<br>Sex: 60-64% F<br>Illness: Schizoaffective/phreniform and schizophrenia<br>Diagnosis: DSM-III-R<br>N: 123<br>Duration of illness:<br>not stated<br>Special characteristics:<br>Depressive and psychotic symptoms combined. 64 (32 each group) with schizoaffective, depressive type; 2 (1 each group) with schizoaffective, bipolar type, 19 (10 R, 9 H/A) with | Intervention:<br>risperidone<br>N: 62<br>Dose:<br>3x 1mg capsules/day dose escalation to 1 week = 8mg/day, thereafter dose altered to take account of side effects/ clinical response (range 2-12mg/day)<br>oral | ESRS changes scores: R +6.2 (8.4) H/A +3.2 (7.2) p=0.034. This was mainly because of a significantly higher shift in the parkinsonism subscale (R +5.8 (7.8) H/A +2.9 (6.4) p=0.028) - no significant changes for dyskinesia or dystonia subscales. Use of concurrent anticholinergic medication: R 37.1%, H/A 19.7%, p=0.05. Any adverse event: R 41/62, H/A 46/61, p=0.35. EPS-like symptoms R 37.1% | |

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| | Comments: Capsules double blind dummy design. | schizophrenia or schizophreniform disorder with major depressive symptoms; 38 (19 each group) with major depression with psychotic features. 9 in R group and 8 in H/A group had comorbid axis II disorder. 38 in R group and 25 in H/A group had been pretreated with antipsychotics, 26 in R and 27 in H/A with antidepressants and 14 in R and 15 in H/A with benzodiazepines.<br>Inclusion/ exclusion criteria:<br>Aged 18-65. Coexisting major depression and paranoid and/or hallucinatory symptoms. PANSS >=60, >=4 on at least 2 PANSS positive subscale items, BRMES >=15 with at least 3 points on depression item. Excluded: history of suicidal tendencies or serious suicide attempt, severe internal or neurologic disease; history of allergic or toxic reaction to psychotropics, participation in clinical trial within 4 weeks, pregnancy.<br>Further details:<br>Not possible to separate results of those with major depression with psychotic features from those with schizophrenia/ affective/ phreniform disorders. | Control:<br>Haloperidol/ amitriptyline<br>N: 61<br>Dose:<br>3x2.5mg capsules/day H, 3x50mg capsules/ day A, dose escalation at 1 week H 10mg, A 200mg, doses then altered according to clinical response/ side effects (range H 2.5-12mg/day, A 50-300mg/day)<br>oral<br><br>Intervention group n:<br>15 dropouts before 3 weeks, 20 before end of study. 13 side-effects, 7 insufficient response (9 protocol deviations)<br><br>Control group n:<br>10 dropouts before 3 weeks, 13 by end of study. 7 side effects, 4 insufficient response, (10 protocol deviations) | H/A 31.1%. Fatigue: R 4 H/A 2. Abnormal hepatic function: R 3 H/A 10. Constipation: R 5, H/A 7. Dry mouth: R 4 H/A 6. Nausea/ vomiting: R 4 H/A 2. Hypotension: R 0 H/A 4. Dizziness: R 2 H/A 1. Hyperprolactinaemia: R 1 H/A 2. Tachycardia: R 1H/A 2. Abdominal pain: R 0 H/A 2. Dysphagia: R 2, H/A 0. SEVERE AEs reported by >1 pt: agitation R 2 H/A 1. Suicidal ideations R 1 H/A 2, akathisia tremor R 2 H/A 0. Speech disorder R 1 H/A 1, dystonia abdominal pain and constipation R 0 H/A 2. Significant increases in body weight occurred in both groups but were less pronounced in the R group (+0.8kg p=0.02) than the H/A group (+2.3kg, p=0.001). No clinically significant ECG changes in either group. No consistent changes in blood chemistry of haematology were observed. | |

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| **Naukkarinen1999/ HGBJ (Finland)** | Duration:<br>Not stated | Age: Not stated<br>Sex: Not stated<br>Illness: schizophrenia<br>Diagnosis: DSM-IV<br>N: 46<br>Duration of illness: not stated<br>Inclusion/ exclusion criteria:<br>At least moderately ill (CGI 4); aged 18-70 years | Intervention:<br>Olanzapine<br>N: 23<br>Dose:<br>5-20 mg/day<br><br>Control:<br>Perphenazine<br>N: 23<br>Dose:<br>8-32 mg/day | Not reported | |
| **Petit1996** | Allocation: random - no further details.*<br>Blinding: double - identical and dummy capsules.<br>Duration: 8 weeks (preceded by omission of last depot injection).<br>Setting: 13 French hospitals.<br>Power calculation: undertaken - to demonstrate an 8.2 difference between treatment groups on BPRS. | Diagnosis: schizophrenia (DSM-III-R).<br>N=126.<br>Age: range 18-68 years, mean ~39.<br>Sex: 73 M, 63 F.*<br>History: currently acutely ill, in hospital, overall duration ill 6 months to 41 years, 4+ on CGI, not physically ill or abusing substances. | 1. Zotepine: dose 150-300mg/day. n=63.<br>2. Haloperidol: dose 10-20mg/day. n=63. | Mental state (50% reduction in BPRS).<br>Leaving the study early.<br>Side effects.<br><br>Unable to use - Global improvement (CGI - no mean or SD).<br>Mental State (SANS - no mean or SD).<br>Side effects (AIMS, SAS - no SD).<br>ECG (no data).<br>Pulse (no SD). | |

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| **Peuskens1995** | Allocation: randomised - 'random permuted block procedure', randomisation list transferred to sealed envelopes.<br>Blindness: double - no further details.<br>Duration: 8 weeks (preceded by 1 week washout).<br>Multi-centre, multi-national. | Diagnosis: schizophrenia (DSM-III-R), PANSS score 60 - 120.<br>N=1362.<br>Age: mean 38.1 years.<br>Sex: female 467, male 894.<br>History: duration of illness, mean 16.8 years, number of previous hospitalisations, median 3, range 1-7, duration of current hospitalisation, median 4 years. | 1. Risperidone: dose 1mg/day. n=229.<br>2. Risperidone: dose 4mg/day. n=227.<br>3. Risperidone: dose 8mg/day. n=230.<br>4. Risperidone: dose 12mg/day. n=226.<br>5. Risperidone: dose 16mg/day. n=224.<br>6. Haloperidol: dose 10mg/day. n=226.<br>Fixed doses after week 1. | Clinical improvement (20% reduction PANSS).<br>Global effect (CGI).<br>Mental state (BPRS - PANSS derived; PANSS).<br>Side effects (CGI, ESRS, modified UKU, use of antiparkinsonian medication).<br>Physiological monitoring (ECG, lab tests).<br>Satisfaction with treatment (categorical scale).<br>Leaving the study early. | |

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| **Puech1998** | *Allocation:*<br>Random – no further details.<br><br>*Blinding:*<br>Double – no further details.<br><br>*Duration:*<br>4 weeks, preceded by a washout period of 3-7 days.<br><br>*Setting:*<br>In-patients. | *Diagnosis:*<br>Schizophrenia (DSM-III-R), disorganised (50%), paranoid (24%) or undifferentiated (26%) types.<br><br>*Age:* Mean 36 years.<br><br>*Sex:* 197 M, 122 F<br><br>*N:* 319<br><br>*History:*<br>Currently acute exacerbation of chronic or subchronic illness. Minimum score of 4 on at least 2 of 4 core positive symptoms. Not treatment resistant. Duration of illness 0- 41 years (mean 10 years). | amisulpride: dose 100mg/day* b.d. n = 61.<br>amisulpride: dose 400mg/day b.d.. n = 64.<br>amisulpride: dose 800mg/day b.d.. n = 65.<br>amisulpride: dose 1200mg/day b.d.. n = 65.<br>haloperidol: dose 16mg/day b.d. n = 64. | Leaving the study early.<br><br>Global state:<br>Response (defined as rating of 1 or 2 on CGI-I scale).<br>Mental state:<br>BPRS total<br>PANSS positive subscale<br>PANSS negative subscale<br><br>Extrapyramidal side effects:<br><br>Prescribed anti-parkinsonian medication.<br>Documented EPS/ scores<br>SAS<br>BAS<br>AIMS<br><br>Other adverse effects:<br>UKU side effects rating scale | |

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| **Purdon2000 (Canada 2000)** | Allocation: randomised, no further details.<br>Blindness: double blind, no further details<br>Duration: 6 months (2 days washout) | Diagnosis: schizophrenia (DSM-IV)<br>Inclusion criteria: no details<br>N=25<br>Age: mean 34 years<br>Sex: M 20, F 5 | Quetiapine modal dose 468mg/day. n=13.<br>Haloperidol modal dose 15.5mg/day n=12. | Global state: CGI<br>Mental state – general: PANSS<br>Mental state - specific: PANSS-P, PANSS-N.<br>Side effects – extrapyramidal, AIMS, Simpson Angus<br>Depressive symptoms – Calgary Depression Scale and Beck Depression Inventory | |
| **Reams 1998/ Kuntz 1998** | Duration:<br>6 weeks | Age: 59 years or older<br>Sex: not stated<br>Illness: combined diagnoses<br>Diagnosis: not stated<br>N: 59<br>Duration of illness:<br>not stated<br>Special characteristics:<br>Elderly<br>Inclusion/ exclusion criteria:<br>Schizophrenia, schizophreniform or schizoaffective disorder | Intervention:<br>Olanzapine<br>N: not stated<br>Dose:<br>5-20mg/day<br><br>Control:<br>Haloperidol<br>N: not stated<br>Dose:<br>5-20mg/day | Treatment-emergent AEs reported by more than 10% participants in olanzapine group were: insomnia, somnolence, and accidental injury.<br>AEs that were reported statistically significantly more often in the haloperidol group were back pain, tremor, akathisia, and rhinitis. | |

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| | | | | No AEs were reported statistically significantly more often in the olanzapine group compared with the haloperidol. The Barnes akathisia score improved on olanzapine but worsened on haloperidol and the treatment difference was statistically significant. | |
| **Study128-302**<br><br>**(now published as Addington *et al.*, 2004)** | Duration:<br>8 weeks<br>Washout:<br>minimum 3 day placebo washout<br>Concomitant medications:<br>Anticholinergics and/ or propranolol were given as needed for EPS. Lorazepam and temazepam were given for agitation and insomnia. | Age: mean 'about' 34 (range 12-54) years<br>Sex: 72% M<br>Illness: combined diagnoses<br>Diagnosis: DSM-III-R<br>N: 296<br>Duration of illness:<br>mean 9 years<br>Special characteristics:<br>chronic or subchronic schizophrenia (88%) or schizoaffective disorder (12%). Not treatment resistant.<br>Inclusion/ exclusion criteria:<br>PANSS total score >=60 and score of >=4 on >=2 of PANSS core items within 25 hours of 1st dose. Aged 18-64. | Intervention:<br>ziprasidone<br>N: 149<br>Dose:<br>80-160mg/day (flexible dose)<br>oral<br><br>Control:<br>risperidone<br>N: 147<br>Dose:<br>3-5mg/day (flexible dose)<br>oral | Withdrawals:<br><br>Intervention group n:<br>Total 55/149 (AE 7, response 22, other 26)<br><br>Control group n:<br>Total 43/147 (AE 11, response 12, other 20) | |

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| | Use of other neuroleptics, antidepressants, lithium and other mood stabilisers was prohibited.<br><br>Comments: Ziprasidone dose titrated up from 80mg if required over 1 week intervals. Risperidone dose titrated up from 1mg to 3mg/day over week 1, then higher in 1mg doses if required. | Exclusion criteria: pregnant or lactating women, mental retardation, organic mental syndromes, organic mental disorders or brief reactive psychosis, significant risk of committing suicide or homicide, history of psychosurgery, history of clinically significant and/or relevant physical illness, fluoxetine within 5 weeks, monoamine oxidase inhibitors (MAOIs) or reversible inhibitors of monoamine oxidase (moclobemide) within 2 weeks, antidepressants or lithium within 1 week of the first day of double-blind therapy, substance abuse/ dependence in previous 3 months, participation in a previous trial with ziprasidone, treatment with an investigational drug during the four weeks immediately preceding the baseline visit.<br>Further details: Patients remained in hospital for days 1-14 but could be discharged after this | | | |

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| **StudyR-0548**<br>(now published as Simpson et al., 2004) | Duration:<br>6 weeks<br>Washout:<br>1 day<br>Concomitant medications:<br>Lorazepam for agitation or insomnia and benztropine for EPS were permitted. Episodic use of antiemetics, chronic use of hypertensives (other than propranolol, reserpine, clonidine and methyldopa), diuretics, Zantac, HRT, oral contraceptives and hypoglycaemics | Age: mean Z 37.7 (9.7), O 37.6 (9.7)<br>Sex: 176 M, 93 F<br>Illness: combined diagnoses<br>Diagnosis: DSM-IV<br>N: 269<br>Duration of illness:<br>13.3 - 14.6 years<br>Special characteristics:<br>schizophrenia (170) or schizoaffective disorder (99), chronic or subchronic, requiring inpatient hospitalisation<br>Inclusion/ exclusion criteria:<br>18-55 years of age, hospitalised for no more than 2 weeks prior to screening, safe outpatient environment, persistent psychotic symptoms for the week prior to hospital admission, scored >=4 on CGI-S, score >=4 on at least one of PANSS positive symptom scale items. Patients with QTc interval of 450msec or more had to be discussed before randomisation. Usual exclusion criteria, including resistance to olanzapine. | Intervention:<br>ziprasidone<br>N: 136<br>Dose:<br>80mg/day days 1-2, 160mg/day days 3-7 then flexible dose<br>Route: oral<br><br>Control:<br>olanzapine<br>N: 133<br>Dose:<br>20mg days 1-2, 40mg days 3-7, then flexible dose<br>Route: oral | Withdrawals:<br><br>Intervention group n:<br>66/136 (adverse events 10, lack of efficacy 12)<br><br>Control group n:<br>49/133 (adverse events 4, lack of efficacy 11) | |

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| **Szafranski1999** | Duration:<br>18 weeks | Age: Not stated<br>Sex: Not stated<br>Illness: schizophrenia<br><br>Diagnosis: DSM-IV<br>N: 95<br>Duration of illness:<br>Not stated<br>Inclusion/ exclusion criteria:<br>Not stated | Intervention:<br>Olanzapine<br>N: not stated<br>Dose:<br>5-20 mg<br><br>Control:<br>Perphenazine<br>N: not stated<br>Dose:<br>8-40 mg<br><br>Intervention group n:<br>56 participants completed the DAI-30 at the end of the study. 30 participants in the olanzapine group and 26 in the perphenazine group.<br><br>Control group n:<br>Patients who did not complete the protocol had more negative symptoms at baseline and after the first week (p<0.05), they also differed in DAI-30 score (more negative attitude) after the first week of treatment (p<005). | Not stated. | |

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| **Tollefson1997** | Allocation: randomised, ratio 2:1 - no further details.<br>Blindness: double - no further details.<br>Duration: 6 weeks (preceded by a screening phase of 2-9 days, maintenance phase of 46/52 for responders). | Diagnosis: schizophrenia, schizophreniform or schizoaffective disorder (DSM-III-R).<br>Inclusion criteria: >18 BPRS Score and/or be intolerant of current antipsychotic medication.<br>N=1996.<br>Age: mean 38.7 years.<br>Sex: male and female. | 1. Olanzapine: dose 5-20mg/day. n=1336.<br>2. Haloperidol: dose 5-20mg/day. n=660.<br>Benztropine & benzodiazepine as required. | Global state (CGI).<br>Mental state (BPRS*, MADRS, PANSS).<br>Mental state (needing additional benzodiazepines).<br>Leaving study early.<br>Side effects (requiring benztropine).<br>Side effects (AMDP, Barnes Akathisia Scale, SAS).<br>Adverse events (COSTART terms).<br><br>Unable to use -<br>Hospital status (no data).<br>Lab tests & physiological measures (no data). | *BPRS (scored 0-6) extracted from PANSS - no reference given for validity of procedure.<br><br>*A priori efficacy response was 40% improvement in BPRS score and three weeks in study. |
| **Gregor1999 (secondary to Tollefson 1997)** | Duration:<br>6 weeks acute phase, then 46 weeks maintenance phase for responders<br><br>Washout:<br>not stated<br>Concomitant medications:<br>not stated | Age: not stated<br>Sex: not stated<br>Illness: schizophrenia<br>Diagnosis: not stated<br>N: 778<br>Duration of illness:<br>not stated<br>Inclusion/ exclusion criteria: not stated | Intervention:<br>olanzapine<br>N: 520<br>Dose:<br>not stated<br><br>Control:<br>haloperidol<br>N: 258<br>Dose:<br>not stated | None reported | |

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| | Comments:<br>Maintenance phase was double blind.<br>Predefined level of response. | | Intervention group n:<br>69.4% completed the acute phase, 52.0% completed the maintenance phase<br><br>Control group n:<br>53.9% completed the acute phase (p<0.001), 35.6% completed the maintenance phase (p=0.005) | | |
| **Hamilton2000 (secondary to Tollefson 1997)** | Duration:<br>6 week acute phase followed by 46 week maintenance phase<br>Washout:<br>yes; length not stated<br>Concomitant medications:<br>Only benzodiazepines for sedation and biperiden or benztropine mesylate for EPS. | Age: Mean (SD): 38 (12) years<br>Sex: 61.1% M<br>Illness: combined diagnoses<br>Diagnosis: DSM-III-R<br>N: 778<br>Duration of illness:<br>Mean (SD): 13.4 (10.8) years<br>Inclusion/ exclusion criteria:<br>At least 18 years old and either had a Brief Psychiatric Rating Scale total score of greater than or equal to 18 and/or were no longer tolerating current neuroleptic (excluding haloperidol) therapy.<br><br>Exclusion: Documented treatment-resistance to neuroleptic agents, | Intervention:<br>Olanzapine<br>N: 520<br>Dose:<br>5-20 mg/day<br><br>Control:<br>Haloperidol<br>N: 258<br>Dose:<br>5-20 mg/day<br><br>Intervention group n:<br>319/520 participants continued on to the maintenance phase.<br>Acute phase completion | Not reported | |

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| | Comments:<br>Initial 5 mg/day dose was increased weekly for participants whose CGI severity score was > 1. Decreases in dose could occur at any time. | DSM-III-R organic mental disorder or substance-use disorder, and/or serious, unstable medical illness.<br>Further details:<br>After completing the acute phase, participants showing a CGI-S score of 3 or less or a decrease in score >=3; a CGI-S (adverse event) score of 3 or more; and clinician judgement that continued treatment was warranted were eligible for continued double-blind therapy in the 46 week maintenance phase. | rate: 69.4%.<br>Reasons: lack of efficacy (17.9%); adverse event (3.7%); participant decision (3.5%).<br>Maintenance phase completion rate: 52.0%.<br>Reasons: adverse events (12.9%); participant decision (10.7%); lack of efficacy (12.5%)<br><br>Control group n: 104/258 participants continued on to the maintenance phase.<br>Acute phase completion rate: 53.9% (p<0.001)<br>Reasons: lack of efficacy (23.3%, p=0.085); adverse event (8.9%, p=0.004); participant decision (7.8%, p=0.013).<br><br>Maintenance phase completion rate: 35.6%, p=0.005.<br>Reasons: adverse events (26.0%, p=0.003); participant decision (19.2%, p=0.08); lack of efficacy (10.6%, p=0.729). | | |

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| **Kinon2000 (secondary to Tollefson 1997)** | Duration:<br>6 weeks<br>Washout:<br>not stated<br>Concomitant medications:<br>not stated<br><br>Comments:<br>For further information see Tollefson 1997 (in HTA report) | Age: not stated<br>Sex: not stated<br>Illness: combined diagnoses<br>Diagnosis: not stated<br>N: 1996<br>Duration of illness:<br>not stated<br>Special characteristics:<br>schizophrenia, schizoaffective disorder or schizophreniform disorder<br>Inclusion/ exclusion criteria:<br>not stated<br>Further details:<br>For further information see Tollefson 1997 (in HTA report) | Intervention:<br>olanzapine<br>N: 1336<br>Dose:<br>5-20mg/day<br>oral<br><br>Control:<br>haloperidol<br>N: 660<br>Dose:<br>5-20mg/day<br>oral | Not reported | |

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| **Tran1997** | Allocation: randomised - no further details.<br>Blindness: double - no further details.<br>Duration: 28 weeks (preceded by 2-9 day washout).<br>Investigators: trained on PANSS. | Diagnosis: schizophrenia, schizophreniform disorder or schizoaffective disorder (DSM-IV).<br>N=339.<br>Age: 16-65 years.<br>Sex: 65% M.<br>Setting: in-patients or out-patients.<br>Exclusion: people who were treatment resistant. | 1. Olanzapine: dose 10-20mg/day. n=172.<br>2. Risperidone: dose 4-12mg/day. n=167.<br>Benzodiazepines, chloral hydrate, benztropine mesylate, biperiden as required. | Mental state (BPRS*, PANSS, SANS).<br>Leaving study early.<br>Side effects (requiring benztropine or biperiden).<br>Side effects (AIMS, Barnes Akathisia Scale, SAS).<br>Side effects (prolactin, low neutrophil counts).<br>Adverse events (AMDP, COSTART list).<br>Quality of life (QOL).<br><br>Unable to use -<br>Global state (CGI - change data).<br>Hospital status (no data).<br>Lab tests & physiological measures (no data).<br>Economic burden (no data). | *BPRS (scored 0-6) extracted from PANSS - no reference given for validity of procedure.<br>PANSS response rates reported >/= 20%,>/= 30%,>/= 40%>/= 50%. |

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| **Ziegler1989** | Duration:<br>4 weeks<br>Washout:<br>3 days<br>Concomitant medications:<br>not stated | Age: mean 35.5 years<br>Sex: not stated<br>Illness: schizophrenia<br>Diagnosis: ICD-9<br>N: 40<br>Duration of illness:<br>not stated<br>Special characteristics:<br>Paranoid and/or delusional disorders. First episode and chronic schizophrenia, positive and negative symptoms.<br>Inclusion/ exclusion criteria:<br>Schizophrenic participants suffering from restlessness requiring heavy doses of neuroleptics were included provided the acute symptoms had decreased and after a washout period/ Excluded: organic brain disorder, intellectual disability, acute somatic disease, participants treated with delayed effect neuroleptics during the previous two weeks. | Intervention:<br>amisulpride<br>N: 20<br>Dose:<br>600mg/day (10)<br>300-750mg/day (10)<br>oral<br><br>Control:<br>Haloperidol<br>N: 20<br>Dose:<br>12mg/day (10)<br>2.5-22.5 mg/day (10)<br>oral<br><br>1 participant receiving haloperidol was withdrawn early. | Webster scale score (cases of EPS):<br>Amisulpride 4/20<br>Haloperidol 11/20<br>($p<0.05$) | |

**References of included studies (previous guideline)**

**Arvanitis1997 (North America 013)**[1]

Arvanitis, L.A., Miller, B.G. and the 'Seroquel' trial 13 study group. (1997). Multiple fixed doses of quetiapine in patients with acute exacerbation of schizophrenia. *Biological Psychiatry, 42,* 233-246.

[1] In the previous guideline, the study was incorrectly cited as being published in 1996.

**Barnas1987**

Barnas C, Stuppäck C, Unterweger B, Hinterhuber H, Fleischhacker WW. (1987) Treatment of negative symptoms in schizophrenia with zotepine. *Journal of Clinical Psychopharmacology*; 7(5): 370-1.

Barnas, C., Stuppäck C.H., Miller, C., Haring, C., et al. (1992). Zotepine in the treatment of schizophrenic patients with prevailingly negative symptoms: a double blind trial vs haloperidol. *International Clinical Psychopharmacology, 7,* 23-27.

**Beasley1996a**

Beasley, C.M., Tollefson, G., Tran, P., Satterlee, W., Sanger, T., Hamilton, S. (1996). Olanzapine versus placebo and haloperidol: Acute phase results of the North American double-blind olanzapine trial. *Neuropsychopharmacology, 14(2),* 111-123.

Tollefson, G. D., Sanger, T. M., Beasley, C. M., Tran, P. V. (1998). A double-blind, controlled comparison of the novel antipsychotic olanzapine versus haloperidol or placebo on anxious and depressive symptoms accompanying schizophrenia. *Biological Psychiatry, 43,*(11) 803-10.

**Beasley1997**

Beasley, C.M., Hamilton, S.H., Crawford, A.M., Dellva, M.A., Tollefson, G.D., Tran, P.V., et al. (1997). Olanzapine versus haloperidol: acute phase results of the international double-blind olanzapine trial. *European Neuropsychopharmacology,7,* 125-37.

**Blin1996**

Blin, O., Azorin, J.M., Bouhours, P. (1996). Antipsychotic and anxiolytic properties of risperidone, haloperidol, and methotrimeprazine in schizophrenic patients. *Journal of Clinical Psychopharmacology, 16(1),* 38-44.

**Carriere2000**

Carriere P, Bonhomme D, Lemperiere T. (2000) Amisulpride has a superior benefit/risk profile to haloperidol in schizophrenia: Results of a multicentre, double-blind study (the Amisulpride Study Group). *European Psychiatry*;15(5):321-329.

**Ceskova1993**

Ceskova E, Svestka J. (1993) Double-blind comparison of risperidone and haloperidol in schizophrenic and schizoaffective psychoses. *Pharmacopsychiatry*; 26(4):121-4.

**Cetin1999**

Cetin M, Ebrinc S, Agargun MY, Basoglu C, Tigit S, Yilmaz V, et al. (1999) Determination of the optimal dose of risperidone in patients with schizophrenia. *European Neuropsychopharmacology*; 9(suppl. 5):S254-S255.

**Chouinard1993**

Chouinard G, Jones B, Remington G, Bloom D, Addington D, MacEwan GW, et al. (1993) A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. *Journal of Clinical Psychopharmacology*, 13(1):25-40.

**Claus1991**

Claus A, Bollen J, De Cuyper H, Eneman M, Malfroid M, Peuskens J, et al. (1992) Risperidone versus haloperidol in the treatment of chronic schizophrenic inpatients: a multicentre double-blind comparative study. *Acta Psychiatrica Scandinavica*, 85(4):295-305.

**Conley2001**

Conley RR, Mahmoud R. (2001) A randomised double-blind study of risperidone and olanzapine in the treatment of schizophrenia or schizoaffective disorder. *Amercian Journal of Psychiatry*, 158(5):765-774.

**Cooper1999a**

Cooper SJ, Tweed J, Raniwalla J, Butler A, Welch C. (2000) A placebo-controlled comparison of zotepine versus chlorpromazine in patients with acute exacerbation of schizophrenia. *Acta Psychiatrica Scandinavica*;101(3):218-25.

**Delcker1990**

Delcker A, Schoon ML, Oczkowski B, Gaertner HJ. (1990) Amisulpride versus haloperidol in treatment of schizophrenic patients: Results of a double-blind study. *Pharmacopsychiatry*;23(3):125-130.

**Dieterle1999**

Dieterle DM, Muller Spahn F, Ackenheil M. (1991) Wirksamkeit und Vertraglichkeit von Zotepin im Doppelblindvergleich mit Perazin bei schizophrenen Patienten. [Effectiveness and tolerance of zotepine in a double-blind comparison with perazine in schizophrenic patients]. *Fortschritte der Neurologie-Psychiatrie*; 59(suppl 1):18-22.

**Fleischhacker1989**

Fleischhacker WW, Barnas C, Stuppack CH, Unterweger B, Miller C, Hinterhuber H. (1989) Zotepine vs. haloperidol in paranoid schizophrenia: a double-blind trial. *Psychopharmacology Bulletin*; 25:97-100.

**Fleischhacker1996 (Multi-country 014)**

Copolov DL, Link CGG, Kowalcyk B. (2000) A multicentre double-blind randomized comparison of quetiapine (ICI 204, 636, Seroquel) and haloperidol in schizophrenia. *Psychological Medicine*; 30(1):95-106.

**Fleurot1997**

Fleurot O, Bech P, Turjanski S, Amisulpride Study Group (1997). Amisulpride versus risperidone in the treatment of acute schizophrenia. In: *Sixth World Congress of Biological Psychiatry*; 22-27 June 1997; Nice, France.

**Gureje1998**

Gureje O, Catts S, Fraser A, Hustig H, Keks N, Lambert Y, et al. (1998) Olanzapine versus risperidone in the treatment of schizophrenia and related psychotic disorders. In: *XXIst Collegium Internationale Neuro-psychopharmacologicum*; 12 -16 July 1998; Glasgow, Scotland.

**Hale2000**

Hale A, Azorin JM, Kasper S, Maier W, Syvalahti E, Van der Burght M, et al. (2000) Sertindole is associated with a low level of extrapyramidal symptoms in schizophrenic patients: Results of a phase III trial. *International Journal of Psychiatry in Clinical Practice*; 4(1):47-54.

Hale A, Azorin JM, Kasper S, Maier W, Syvalahti E, Van der Burght M, et al. (2000) Sertindole improves both the positive and negative symptoms of schizophrenia: Results of a phase III trial. *International Journal of Psychiatry in Clinical Practice*; 4(1):55-62.

**HGBL1997 unpublished**

HGBL 1997. Eli Lilly. Data on file. Data supplied to the Cochrane Schizophrenia Group 1999.

**HGCJ1999**

HGCJ (Hong Kong) 1999. (unpublished). Eli Lilly and Company Limited.

**HGCU(Taiwan) 1998**

HGCU (Taiwan) 1998. (unpublished). Eli Lilly and Company Limited.

**Hillert1994**

Hillert A, Philipp M, Gattaz WF, et al. (1994) Amisulpride vs flupentixol in the treatment of schizophrenia with predominant positive symptomatology: a controlled double-blind study. *Neuropsychopharmacology*; 10(suppl. Part 2):31.

**Hoyberg1993**

Hoyberg OJ, Fensbo C, Remvig J, Lingjaerde O, Sloth-Nielsen M, Salvesen I. (1993) Risperidone versus perphenazine in the treatment of chronic schizophrenic patients with acute exacerbations. *Acta Psychiatrica Scandinavica*; 88:395-402.

**Huttenen1995**

Huttunen M, Piepponen T, Rantanen H, Larmo I, Nyholm R, Raitasuo V. (1995) Risperidone versus zuclopenthixol in the treatment of acute schizophrenic episodes: a double-blind parallel-group trial. *Acta Psychiatrica Scandinavica*; 91:271-7.

**Jakovljevic1999**

Jakovljevic M, Dossenbach MR, Friedel P, Schausberger B, Grundy SL, Hotujac L, et al. (1999) Olanzapine versus fluphenazine in the acute (6-week) treatment of schizophrenia. *Psychiatria Danubina*; 11(1-2):3-11.

**Janicak1999**

Janicak PG, Davis JM, Kasckow JW, Tugrul K, Dowd RNS, Sharma RP. (1999) Risperidone versus haloperidol for schizoaffective disorder. In: *152nd Annual Meeting of the American Psychiatric Association*; 15 - 20 May 1999; Washington DC.

**Klieser1996**

Klieser E, Lehmann E, Heinrich K. Risperidone in comparison with various treatments of schizophrenia (1996). In: Kane JM, Moller HJ, Awouters F, eds. Serotonin in antipsychotic treatment: *Mechanisms and Clinical Practice*. New York: Marcel Dekker.

**KnollCTR (Study ZT4002)**

Laboratoires Knoll France. (2001) *Multicentre, double blind, parallel-group comparative study of zotepine versus haloperidol, evaluating costs, quality of life and efficacy in patients with chronic or subchronic schizophrenia*. Report No: Study No. ZT 4002. Levallois-Perret: Laboratoires Knoll France.

**Lecrubier2000**

Lecrubier Y, Benkert O, Kasper S, Peuskens J, Sechter D. (2000) Amisulpride versus risperidone in schizophrenia: comparing clinical and functional outcome in a six month study. In: *39th Annual Meeting of the American College of Neuropsychopharmacology;* December 10-14 2000; San Juan, Puerto Rico. Available from: URL: http://www.acnp.org/AOLGATE/default.htm#

**Link1994 (Europe-Africa 007)**

Peuskens J, Link CG. (1997) A comparison of quetiapine and chlorpromazine in the treatment of schizophrenia. *Acta Psychiatrica Scandinavica*; 96(4):265-73.

**Liu2000**

Liu SK, Chen WJ, Chang CJ, Lin HN. (2000) Effects of atypical neuroleptics on sustained attention deficits in schizophrenia: a trial of risperidone versus haloperidol. *Neuropsychopharmacology*; 22(3):311-9.

**Loza1999**

Loza N, El-Dosoky AM, Okasha TA, Khalil AH, Hasan NM, Dossenbach M, et al. (1999) Olanzapine compared to chlorpromazine in acute schizophrenia. *European Neuropsychopharmacology*; 9(suppl 5):S291.

**Malyarov1999**

Malyarov S, Dzub G. (1999) Comparative assessment of the positive and negative symptom dynamics in schizophrenic patients treated with atypical antipsychotics or haloperidol. *European Neuropsychopharmacology*; 9(suppl. 5):S296.

**Marder1994**

Marder SR, Meibach RC. (1994) Risperidone in the treatment of schizophrenia. *American Journal of Psychiatry*; 151 (6 suppl):825-35.

**Mesotten1991**

Mesotten F, et al. (1991) *Risperidone versus haloperidol in the treatment of chronic psychotic patients: a multicentre double-blind study*. Clinical Research Report No: RIS-INT-2, N85163. Piscataway, NJ: Janssen.

**Min1993**

Min SK, Kim DK. (2000) Effects of haloperidol and risperidone on the quality of life of chronic schizophrenic patients. *International Journal of Neuropsychopharmacology*; 3(suppl. 1):101-S101.

**Moller1997**

Moller HJ, Boyer P, Rein W, Eich FX, Group AS. (1997) Treatment of schizophrenic patients with acute exacerbations: A double-blind comparison of amisulpride and haloperidol. *Pharmacopsychiatry* 30 (5): 199.

**MullerSiecheneder1998**

Muller Siecheneder F, Muller MJ, Hillert A, Szegedi A, Wetzel H, Benkert O. (1998) Risperidone versus haloperidol and amitriptyline in the treatment of patients with a combined psychotic and depressive syndrome. *Journal of Clinical Psychopharmacology*;18(2):111-20.

**Naukkarinen1999/ HGBJ (Finland)**

Naukkarinen H, Rimon R, Katila H, Riihikangas R, Heikkila L. (2000) Olanzapine and perphenazine in schizophrenia. *Schizophrenia Research*;41(1):190.

**Petit1996**

Petit M, Raniwalla J, Tweed J, Leutenegger E, Dollfus S, Kelly F. (1996) A comparison of an atypical and typical antipsychotic, zotepine versus haloperidol in patients with acute exacerbation of schizophrenia: a parallel-group double-blind trial. *Psychopharmacology Bulletin*; 32:81-87.

**Peuskens1995**

Peuskens J. (1995) Risperidone in the treatment of patients with chronic schizophrenia: A multi-national, multi-centre, double-blind, parallel-group study versus haloperidol. *British Journal of Psychiatry*; 166(6): 712-726.

**Puech1998**

Puech AJ. (1998) Amisulpride, an atypical antipsychotic, in the treatment of acute episodes of schizophrenia. *Acta Psychiatrica Scandinavica*;98:65-72.

**Purdon2000 (Canada 2000)**

Purdon SE, Malla A, Labelle A, Litt W. (2000) Neuropsychological change in schizophrenia after 6 months of double-blind treatment with quetiapine or haloperidol. *Schizophrenia Research*; 41(1):205-206.

Purdon SE, Malla A, Labelle A, et al. (2001) Neuropsychological change in patients with schizophrenia after treatment with quetiapine or haloperidol. *Journal of Psychiatry and Neuroscience*; 26(2):137-49.

**Reams1998**

Reams SG, Sanger TM, Beasley CM. (1998) Olanzapine in the treatment of elderly patients with schizophrenia and related psychotic disorders. *Schizophrenia Research*; 29(1-2):151-152.

Kuntz AJ, Sanger TM, Beasley CM. (1998) Olanzapine in the treatment of elderly patients with schizophrenia and related psychotic disorders. In*: 11th Annual Meeting of the American Association for Geriatric Psychiatry*; 8 -11 March 1998; San Diego, California, USA.

**Study128-302 (unpublished)**

Pfizer (1997). *Eight week multicentre double-blind study comparing ziprasidone with risperidone in the treatment of patients with acute exacerbation of schizophrenia or schizoaffective disorder.* Report No: 128-302. Sandwich: Pfizer, 8 May, 1997.

**StudyR-0548 (unpublished)**

Pfizer (2001). Appraisal on newer (atypical) antipsychotic drugs in the treatment of schizophrenia: supplementary information. Submission for ziprasidone. Sandwich: Pfizer, 8 June, 2001.

**Szafranski1999**

Szafranski T, Jarema M, Olajossy M, Chzanowski W, Araszkiewicz A, Landowski J, et al. (1999) Subjective experiences of schizophrenic patients on atypical antipsychotic olanzapine and typical antipsychotic perphenazine. *European Neuropsychopharmacology*;9 (suppl. 5):S273.

**Tollefson1997**

Tollefson GD, Beasley CM, Tran PV, Street JS, Krueger JA, Tamura RN, et al. (1997) Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. *American Journal of Psychiatry;* 154:457-65.

Gregor KJ, Hamilton SH, Edgell ET. (1999) Functional outcomes in schizophrenia: a European comparison of olanzapine and haloperidol. *European Neuropsychopharmacology*; 9(suppl. 5):S289.

Hamilton SH, Edgell ET, Revicki DA, Breier A. (2000) Functional outcomes in schizophrenia: A comparison of olanzapine and haloperidol in a European sample. *International Clinical Psychopharmacology;* 15(5):245-255.

Kinon BJ, Roychowdhury SM, Milton DR, Hill AL. (2001) Effective resolution with olanzapine of acute presentation of behavioral agitation and positive psychotic symptoms in schizophrenia. *Journal of Clinical Psychiatry*; 62(Suppl 2):17-21.

**Tran1997**

Tran PV, Hamilton SH, Kuntz AJ, Potvin JH, Andersen SW, Beasley C, et al. (1997) Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. *Journal of Clinical Psychiatry*; 17(5):407-418.

**Ziegler1989**

Ziegler B. (1989) Study of the efficacy of a substituted benzamide, amisulpride versus haloperidol in productive schizophrenia. In: Borenstein P, ed. *Amisulpride: Expansion Scientifique Française*, pp. 73-81. Paris.

**Characteristics of included studies (update)**

| **Study ID** | **ATMACA2002** |
|---|---|
| **General info** | **Funding source:** Not mentioned |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** ITT All participants were analysed due to 0 dropout |
| | **Blindness:** No mention |
| | **Duration:** No. weeks of treatment 6 |
| | **Raters:** Not stated to be independent of treatment |
| | **Design:** Single-centre Turkey |
| | **Number of people screened, excluded & reasons:** No mention |
| | **Notes about study methods:** Randomisation procedures not reported |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 100% |
| | **Diagnostic tool:** ICD-10 |
| | **Inclusion criteria:**<br>- Female<br>- Aged 18–45<br>- Had been attended to for the first time at the Firat University School of Medicine Department of Psychiatry between October and December 2000, and diagnosed with schizophrenia according to DSM-IV. |
| | **Exclusion criteria:**<br>- Severe physical illness<br>- History of alcohol and substance abuse or dependence<br>- Presence of any endocrinologic state<br>- Taking oral contraceptives. |
| | **Total sample size:** No. randomised 35 |
| | **Gender:** % female 100% |
| | **Age:** Mean Quetiapine: 27.62 (9.23)<br>Haloperidol: 29.44 (10.08) |
| | **Ethnicity:** Not mentioned |

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| | **Setting:** Outpatient |
| | **History:** No significant difference between groups |
| | **Baseline stats:** Two groups were matched according to previous hospitalization numbers, duration of hospitalization, mean duration of illness, and mean age of onset (p > 0.05). |
| **Interventions** | **Intervention - group 1.:** Quetiapine, 600mg/day; n=18 |
| | **Intervention - group 2.:** Haloperidol, 10mg/day; n=17 |
| | **Notes about the interventions:** Study medications were initiated after a 2-week washout period. |
| **Outcomes** | **Leaving the study early:** Leaving due to any reason (non-adherence to study protocol) |
| | **Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - BPRS, PANSS |
| | **Adverse events:** Number of people with specific adverse effects - Galactorrhoea |
| | **Adverse events:** Average score/change in specific adverse effects ESRS |
| | **Other:** Prolactin levels |
| **Quality** | **1.1 The study addresses an appropriate and clearly focused question.:** Well covered |
| | **1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately |
| | **1.3 An adequate concealment method is used.:** Not addressed |
| | **1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Not addressed |
| | **1.5 The treatment and control groups are similar at the start of the trial.:** Adequately addressed |
| | **1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed |
| | **1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered |
| | **1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** <20% |
| | **1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Not applicable |
| | **1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not applicable |
| | **2.1 How well was the study done to minimise bias?:** + |

| | |
|---|---|
| **Study ID** | **AZORIN2006** |
| **General info** | **Funding source:** Pharmaceutical industry |

| | |
|---|---|
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** ITT- All patients exposed to treatment and with at least one evaluation after baseline. |
| | **Type of analysis:** Observed case |
| | **Type of analysis:** LOCF |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment 12 |
| | **Raters:** Not stated to be independent of treatment |
| | **Design:** Multi-centre 70 centres in France |
| | **Number of people screened, excluded & reasons:** 263 patients screened. 76 were excluded. 1 participant did not receive any study drug - reasons not given |
| | **Notes about study methods:** Randomisation procedure not reported. |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 100 |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:**<br>- Aged 18-65<br>- DSM-IV schizophrenia of the paranoid, disorganised, catatonic or undifferentiated type.<br>- Baseline score >2 for at least two of the four PANSS items and with a sum of any two of these four items >=8<br>- At least moderately ill on the CGI-S<br>- Antipsychotic-treatment naive or had shown a beneficial response to such treatment at any time in the past 5 years. |
| | **Exclusion criteria:**<br>- If screening ECG showed a QT interval of >=430s for males and >=450s for females. |
| | **Total sample size:** No. randomised 187 |
| | **Total sample size:** ITT population 172 |
| | **Gender:** % female 39 |
| | **Age:** Mean 35 |
| | **Ethnicity:** 97% Caucasian, 2% Black, 0.5% Asian, .05% Other |
| | **Setting:** Outpatient |
| | **Setting:** Inpatient |
| | **History:** Years of illness not reported |

**Baseline stats:**
[Sertindole / Risperidone]
PANSS: 67.9 (18.5) / 69.3 (14.9)
CGI-S: 5.1 (0.6) / 5.2 (0.7)
DAI: 29.8 (5.8) / 31.0 (6.1)
GAF: 37.9 (12.3) / 37.2 (10.5)

**Interventions**

**Intervention - group 1.:** sertindole, 12-24mg/day; n=90

**Intervention - group 2.:** Risperidone, 4-10mg/day; n=82

**Notes about the interventions:**
Prior to start of treatment, 4–7-day placebo washout period during which patients were given placebo capsules only.

Sertindole
-In the titration period (days 1–16), sertindole was
administered once daily; the initial 4mg/day dose was
increased by 4 mg every fourth day up to 16mg
After the titration period (day 16) - flexible dosages of 12-24mg daily.
-Mean daily dose = 16.2mg

Risperidone
-In the titration period (days 1–16) - 1mg twice a day and
then increased by 2 mg every day to 6mg until the end of the titration period.
After the titration period - 4–10mg/day
-Mean daily dose = 6.6mg

Treatment with either drug consisted of two capsules twice daily regardless of dose, using placebo as
necessary to maintain the blind.

Concomitant treatment with lorazepam or oxazepam up
to a dose of 7.5 mg/day or 150 mg/day, respectively, was
permitted. Biperidene up to a dose of 8 mg/ day permitted. If diuretic treatment was needed, a potassium-sparing diuretic was allowed.

**Outcomes**

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Leaving the study early:** Leaving because of adverse effects

**Global state & service outcomes (e.g. CGI):** Average score/change in global state - CGI-S, CGI-I, GAF

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS

**Mental state (e.g. BPRS, PANSS, BDI):** Clinically significant response in mental state - Proportion achieving >=10-50% improvement in PANSS

**Adverse events:** Number of people with general adverse effects

**Adverse events:** Average score/change in specific adverse effects - SAS; BAS; AIMS; ECGs measuring changes in QT intervals

**Adverse events:** Number of people with specific adverse effects

**Satisfaction with treatment:** Service user satisfaction - DAI

**Other:** BMI

**Quality**

**1.1 The study addresses an appropriate and clearly focused question.:** Well covered

**1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately

**1.3 An adequate concealment method is used.:** Not addressed

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered

**1.5 The treatment and control groups are similar at the start of the trial.:** Well covered

**1.6 The only difference between groups is the treatment under investigation.:** Not addressed

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** 20-50%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Well covered

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not addressed

**2.1 How well was the study done to minimise bias?: +**

**Study ID**

**BREIER2005**

**General info**

**Funding source:** Pharmaceutical industry

**Published or unpublished data?:** Published

**Method**

**Type of study:** Individual randomised trial

**Type of analysis:** ITT - population not defined.

**Type of analysis:** LOCF

**Blindness:** Double-blind

**Duration:** No. weeks of treatment *28*

**Raters:** Not stated to be independent of treatment

**Design:** Multi-centre - 12 sites in Europe, North and South America

**Number of people screened, excluded & reasons:** Not reported

**Notes about study methods:** Randomisation procedure not reported

**Participants**

**Diagnosis:** Schizophrenia [% of sample] 100%

**Diagnostic tool:** DSM-IV

**Inclusion criteria:**
- Age 18-75
- BPRS >=42; score >=4 on at least one positive symptom item on PANSS; CGI >=4

**Exclusion criteria:**
- participated in a clinical trial of another drug within 1 month before study entry.
- treated with injectable depot antipsychotic drug within one treatment cycle before study entry; if treated with Clozapine within 7 days before enrolment
- used olanzapine or ziprasidone within 6 months and had treatment withdrawn due to clinically important and/or intolerable adverse effects or exhibited a lack of treatment response
-QTc interval longer than 500msec; any ECG abnormalities at visit 1 or 2
-DSM-IV substance dependence within the past month
-any serious, unstable illness

**Total sample size:** No. randomised 548

**Total sample size:** ITT population Not clearly stated

**Gender:** % female 46%

**Age:** Mean 39

**Ethnicity:** Caucasian (43.6%)
African Descent (26.3%)
Hispanic (22.6%)
Other (7.5%)

**Setting:** Outpatient

**Setting:** Inpatient

**History:**
[Olanzapine / Ziprasidone]
Age at onset: 40.1(11.6) / 38.2(12.1)

Number of previous episodes: 7.0(6.8) / 6.6(7.2)

**Baseline stats:**
[Olanzapine / Ziprasidone]
PANSS: 99.8(19.1) / 102.0(21.2)
CGI: 4.8(0.7) / 4.8(0.8)
MADRS: 15.9(9.3) / 15.9(9.1)
Ham-D: 11.3(6.9) / 11.3(6.7)
Heinrichs-Carpenter QoL: 45.8(19.8) / 43.5(20.3)

**Interventions**

**Intervention - group 1.:** Olanzapine: 10-20mg/day; n=277

**Intervention - group 2.:** Ziprasidone: 80-160mg/day; n=271

**Notes about the interventions:**
2-9 day screening, washout and single-blind placebo lead-in period. Lorazepam (<=4mg/day) was permitted during the washout period. Benzodiazepine or hypnotic monotherapy was permitted, although those requiring more than two concurrent Benzodiazepine hypnotic medications were removed.

Olanzapine
- 10mg/day stable after 3 days. Thereafter, dose could be increased by 5mg/day each visit to a maximum of 20 mg/day. Dose could be reduced by same increment; however, patients were discontinued if they could not tolerate the minimum dose of 10mg/day
- Mean modal dose = 15.27(4.52) mg/day

Ziprasidone:
- started at 20mg b.i.d. After 3 days, increased to 40mg b.i.d Thereafter, the dose could be increased by 40mg/day to a maximum of 160 mg/day. The dose could be reduced by same increment; however, patients were discontinued if they could not tolerate the minimum dose of 80 mg/day.
- Mean modal dose = 115.96 (39.91) mg/day

Benzotropine mesylate or biperiden permitted up to 6mg/day

**Outcomes**

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Leaving the study early:** Leaving because of adverse effects

**Global state & service outcomes (e.g. CGI):** Clinically significant response in global state CGI- % participants with symptom exacerbation defined as a worsening in the CGI severity of illness score of >=1 point after 8 weeks

**Global state & service outcomes (e.g. CGI):** Average score/change in global state CGI

**Mental state (e.g. BPRS, PANSS, BDI):** Clinically significant response in mental state PANSS - % responders defined as a 30% improvement

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|---|---|
| | **Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS; MADRS; Ham-D; |
| | **Adverse events:** Number of people with general adverse effects |
| | **Adverse events:** Number of people with specific adverse effects |
| | **Adverse events:** Average score/change in specific adverse effects - AIMS; Simpson-Angus rating scale; BARS |
| | **Quality of Life:** Average score/change in quality of life - Heinrichs-Carpenter QoL |
| | **Other:** - fasting glucose; lipid levels; weight; prolactin level; and QTc interval |
| **Quality** | **1.1 The study addresses an appropriate and clearly focused question.:** Adequately addressed |
| | **1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately |
| | **1.3 An adequate concealment method is used.:** Not addressed |
| | **1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered |
| | **1.5 The treatment and control groups are similar at the start of the trial.:** Adequately addressed |
| | **1.6 The only difference between groups is the treatment under investigation.:** Not addressed |
| | **1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered |
| | **1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** 20-50% |
| | **1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Not reported adequately |
| | **1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not addressed |
| | **2.1 How well was the study done to minimise bias?: +** |

| | |
|---|---|
| **Study ID** | **CHAN2007B** |
| **General info** | **Funding source:** Pharmaceutical industry |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** LOCF |
| | **Type of analysis:** ITT all randomised participants |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment 4 |

**Raters:** Independent of treatment

**Design:** Multi-centre 5 medical centres in Taiwan

**Number of people screened, excluded & reasons:** 95 screened, of these 10 were not randomised due to the following: withdrew consent (4), withdrawn by investigator (2), family refused (2), used long-acting antipsychotics (2), PANSS total <60 (1) and wrong diagnosis (1)

**Notes about study methods:** Randomisation ratio of 3:2 (aripiprazole: risperidone) using permuted block randomisation stratified by centre. No further details reported.

**Participants**

**Diagnosis:** Schizophrenia [% of sample] 96%

**Diagnosis:** Other schizophrenia related [%] Schizoaffective disorder - 4%

**Diagnostic tool:** DSM-IV

**Inclusion criteria:**
- men and nonpregnant, nonlactating women with a primary diagnosis of schizophrenia or schizoaffective disorder and were hospitalised for an acute relapse
- aged 18-65
- evidence of response to antipsychotic medication e.g. had shown an improvement with an antipsychotic other than clozapine and had been an outpatient for at least one 3-month period during the past year
- PANSS total >=60, minimum of 4 on >=2 PANSS positive subscale items
- patients taking long-acting neuroleptic treatment could be included if a time period of at least 1 treatment cycle plus 1 week had elapsed since last injection.

**Exclusion criteria:**
- psychiatric disorder other than schizophrenia or schizoaffective disorder requiring pharmacotherapy
- serious suicidal ideations
- first episode of schizophrenia or schizoaffective disorder
- clinically significant neurological abnormality other than tardive dyskinesia or EPS
- current diagnosis of psychoactive substance dependence or a history of drug or alcohol abuse within 1 month prior to study
- any unstable medical condition, or treatment with an investigation drug within 4 weeks prior to start.

**Total sample size:** No. randomised - 83

**Total sample size:** ITT population - 83

**Gender:** % female 46%

**Age:** Mean 35

**Ethnicity:** Not reported

**Setting:** Inpatient

**History:**

[Aripiprazole / Risperidone]
No. of previous psychotic episodes: 3.1(2.2) / 2.8(1.9)

**Baseline stats:**
[Aripiprazole / Risperidone]
PANSS total: 85.1(15.7) / 84.6(17.0)
PANSS positive: 22.6(4.6) / 20.0(4.3)
PANSS negative: 22.0(6.3) / 21.3(6.5)
CGI-S: 5.0(0.7) / 5.1(0.7)

**Interventions**

**Intervention - group 1.:** Aripiprazole, 15mg/day; n=49

**Intervention - group 2.:** Risperidone, 6mg/day; n=34

**Notes about the interventions:**
Participants meeting the inclusion criteria underwent a 3-day placebo washout period.
- Risperidone dosing regimen was selected on the basis of the drug's package insert and clinical practice. Doses were titrated upward: 2mg day 1, 4mg day 2 and 6mg thereafter. Doses were administered twice orally.
- Aripiprazole was given as a fixed full dose orally in the morning, with a placebo in the evening to maintain double-blind.
- Doses were fixed throughout the study and could not be increased for lack of efficacy or decreased for the occurrence of AEs.
- Use of psychotropic drugs other than those in the protocol was prohibited with the exception of benzodiazepines for anxiety and insomnia.

**Outcomes**

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Leaving the study early:** Leaving because of adverse effects

**Global state & service outcomes (e.g. CGI):** Average score/change in global state CGI

**Global state & service outcomes (e.g. CGI):** Clinically significant response in global state CGI-I score <=2 (response criteria was not set a priori)

**Mental state (e.g. BPRS, PANSS, BDI):** Clinically significant response in mental state - >=30% decrease in PANSS total score (response criteria was not set a priori)

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS

**Adverse events:** Average score/change in specific adverse effects- BAS; SAS; AIMS

**Adverse events:** Number of people with specific adverse effects - Includes table of AEs experienced by >5%. Most common AEs included insomnia, psychotic disorder, EPS, vomiting, constipation and dizziness

**Adverse events:** Number of people with general adverse effects

**Other:** Vital signs; body weight; significant weight gain; ECG; and laboratory tests.

**Quality**

**1.1 The study addresses an appropriate and clearly focused question.:** Well covered

**1.2 The assignment of subjects to treatment groups is randomised.:** Adequately addressed

**1.3 An adequate concealment method is used.:** Not addressed

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered

**1.5 The treatment and control groups are similar at the start of the trial.:** Adequately addressed

**1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** 20-50%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Well covered

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Adequately addressed

**2.1 How well was the study done to minimise bias?: +**

| **Study ID** | **DAVIDSON2007** |
|---|---|
| **General info** | **Funding source:** Pharmaceutical industry |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** ITT - Patients who received at least one dose of study medication and had at least one post-baseline efficacy assessment. |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment 6 |
| | **Raters:** Not stated to be independent of treatment |
| | **Design:** Multi-centre - 74 centres in North America and Canada (31), Eastern Europe (17), Asia (12), Israel (5), Mexico (5) and South Africa (4) |
| | **Number of people screened, excluded & reasons:** 732 people screened, 114 failed inclusion/exclusion criteria |
| | **Notes about study methods:** Randomisation was balanced by using permuted blocks of treatment and stratified by study centre. No further details reported. |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 100% |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:**<br>- >=18 years |

- DSM-IV diagnosis of schizophrenia for at least 1 year prior to screening and experiencing an acute episode as represented by PANSS total score of 70-120
- agree to voluntary hospitalisation for a minimum of 14 days

**Exclusion criteria:**
- diagnosis of substance dependence within previous 6 months
- medical condition which could affect absorption, metabolism or excretion of study drug
- history of tardive dyskinesia or neuroleptic malignant syndrome
- significant risk of suicide or violent behaviour
- pregnant or breastfeeding female participants
- patients receiving a depot antipsychotic within 120 days of screening or paliperidone palmitate as part of a clinical trial within 10 months before screening.
-a history of drug sensitivity or allergy including hypersensitivity to risperidone, paliperidone, or olanzapine; history of unresponsiveness to antipsychotics.

**Total sample size:** No. randomised 618

**Total sample size:** Safety population 614

**Total sample size:** ITT population 605

**Gender:** % female 32%

**Age:** Mean 36.8(10.6)

**Ethnicity:** White: 49%
Black: 21%
Asian: 24%
Other: 6%

**Setting:** Inpatient All participants were required to agree to voluntary hospitalisation for at least the first 14 days of the trial.

**Setting:** Outpatient

**History:**
[Placebo / Paliperidone 3mg / 9mg / 15mg / olanzapine 10mg]
Age at diagnosis: 24.5(9.2) / 25.7(8.2) / 25.2(8.5) / 25.2(7.8) / 24.6(8.0)
Number of previous hospitalisations (%)
None: 12 / 15 / 18 / 10 / 9
One: 34 / 28 / 19 / 20 / 26
Two: 13 / 15 / 22 / 25 / 19
Three: 13 / 16 / 14 / 13 / 10
>=four: 29 / 25 / 28 / 32 / 36

**Baseline stats:**
[Placebo / Paliperidone 3mg / 9mg / 15mg / olanzapine 10mg]
PANSS total: 93.9(12.7) / 91.6(12.2) / 93.9(13.2) / 92.3(12.3) / 93.3(12.2)
PANSS positive: 28.3(4.9) / 27.4(4.9) / 28.4(5.5) / 27.6(5.1) / 27.8(4.7)
Negative: 23.0(5.4) / 21.4(4.3) / 22.0(4.8) / 21.3(4.8) / 21.8(4.1)

**Notes about participants:**
[Placebo / Paliperidone 3mg / 9mg / 15mg / olanzapine 10mg]
Previous antipsychotic therapy*
Atypical: 57 / 61 / 59 / 56 / 61
Conventional: 58 / 55 / 58 / 55 / 55

*within 3 months prior to screening

**Interventions**

**Intervention - group 1.:** Paliperidone Extended release, 3mg; n=123

**Intervention - group 2.:** Paliperidone ER, 9mg; n=123

**Intervention - group 3.:** Paliperidone ER, 15mg; n=113

**Intervention - group 4.:** Placebo; n=120

**Intervention - group 5:** Olanzapine, 10mg; n=126

**Notes about the interventions:**
During a 5-day screening period, patients included in the study discontinued prior medications, including antipsychotic medication, antiparkinsonian drugs, beta-blockers and prescription, herbal or over-the-counter psychotropics, for 3 days before randomisation.
- Permitted rescue medication included benzodiazepine up to equivalent of 6mg lorazepam during screening and week 1, <=3mg during week 2 and at a dose not to exceed pre-study dose or 2mg/day (whichever was lower) for weeks 3-6. Antidepressant use was also permitted for patients on a stable dose for 3 months prior to study.
- The 3 and 9mg doses were maintained throughout the study. The 15mg.day group started on 12mg for week 1 and then 15mg weeks 2-6.
- The Olanzapine group was included to provide a concurrent active control in order to confirm the study was adequate to detect a drug effect in the event of a negative finding for paliperidone. The study was not designed to support comparisons between paliperidone ER and olanzapine.

**Outcomes**

**Leaving the study early:** Leaving because of adverse effects

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Global state & service outcomes (e.g. CGI):** Clinically significant response in global state - % classified as 'marked' or 'severely ill'

**Global state & service outcomes (e.g. CGI):** Average score/change in global state - CGI

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS total and Marder factors

**Mental state (e.g. BPRS, PANSS, BDI):** Clinically significant response in mental state - Clinical response defined as a >=30% reduction in

| | |
|---|---|
| | PANSS total score from baseline to endpoint |
| | **General and psychosocial functioning (e.g. SFS):** Average score/change in general functioning - PSP |
| | **Adverse events:** Number of people with general adverse effects |
| | **Adverse events:** Number of people with specific adverse effects - Reports AEs experienced by >=5% of participants. Most common AES included insomnia, headache and tachycardia |
| | **Adverse events:** Average score/change in specific adverse effects - AIMS; BAS; SAS |
| | **Other:** % using rescue medications; onset of therapeutic effect; clinical laboratory tests including haematology, fasting serum chemistry including fasting glucose, lipids and prolactin levels; bodyweight; significant bodyweight change; ECG and vital signs. |
| **Quality** | **1.1 The study addresses an appropriate and clearly focused question.:** Well covered |
| | **1.2 The assignment of subjects to treatment groups is randomised.:** Adequately addressed |
| | **1.3 An adequate concealment method is used.:** Not addressed |
| | **1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered |
| | **1.5 The treatment and control groups are similar at the start of the trial.:** Well covered |
| | **1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed |
| | **1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered |
| | **1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** 20-50% |
| | **1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Well covered |
| | **1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Adequately addressed |
| | **2.1 How well was the study done to minimise bias?: +** |

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|---|---|
| **Study ID** | **HWANG2003** |
| **General info** | **Funding source:** Pharmaceutical industry |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** ITT - All participants who were randomised and successfully completed placebo washout phase |
| | **Type of analysis:** LOCF |

**Blindness:** Double-blind

**Duration:** No. weeks of treatment 6

**Raters:** Not stated to be independent of treatment

**Design:** Multi-centre Four centres in Taiwan

**Number of people screened, excluded & reasons:** 48 randomised, 1 withdrew during placebo washout period

**Notes about study methods:** Randomisation details not reported

**Participants**

**Diagnosis:** Schizophrenia [% of sample] 100

**Diagnostic tool:** DSM-IV

**Inclusion criteria:**
- 18-65 years old
- Scoring 4 or above for at least 2 out of the 7 positive symptoms in the PANSS
- PANSS total score between 60-120

**Exclusion criteria:**
- History of allergy or hypersensitivity to risperidone, benzamides, procyclidine or benzodiazepines
- significant neurological diseases such as stroke, Parkinson's disease or epilepsy
- significant organic brain syndrome
- history of severe medical diseases such as cardiovascular, renal or liver diseases.
- pregnancy, lactation, or intention to become pregnant
- recent abuse of psychoactive drugs or alcohol
- placebo response during placebo run-in period e.g. PANSS score reduced by 40%+

**Total sample size:** No. randomised 48

**Total sample size:** ITT population 47

**Gender:** % female 57.5

**Age:** Mean 35

**History:** Mean duration of illness = 13.3yrs

**Baseline stats:**
[Amisulpride / Risperidone]
PANSS: 93.1 (11.5) / 89.9 (14.1)
BPRS: 52.5 (5.9) / 51.1 (7.9)
CGI: 4.7 (0.6) / 4.6 (0.7)
SOFAS: 36.2 (8.3) / 38.8 (9.9)

**Notes about participants:** - placebo run-in (washout) period of 3 to 6 days.

- Those receiving a depot injection were required to have a minimal washout period equivalent to the previous injection interval

**Interventions** **Intervention - group 1.:** Amisulpride (400 - 800mg/day); n=22
- 400mg/day for the first 6 days. Subsequently, the drug was titrated according to clinical response at the discretion of the investigators.
- Mean dose after 28 days remained constant at 630mg (150mg)/ day

**Intervention - group 2.:** Risperidone (4-8mg/day); n=25
- doses were titrated from 1mg/day to 4mg/day during the first 6 days.
- Subsequently the drug was titrated according to clinical response at the discretion of the investigators.
- Mean dose at 28 days = 6.56 (1.58) mg/day
- Mean dose at 42 days = 6.88 (1.54) mg/day

**Notes about the interventions:** Both drugs were provided in identical sealed capsules

**Outcomes** **Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Global state & service outcomes (e.g. CGI):** Average score/change in global state - CGI

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS, BPRS

**Mental state (e.g. BPRS, PANSS, BDI):** Clinically significant response in mental state - Responder defined as >=20% reduction in PANSS Total

**General and psychosocial functioning (e.g. SFS):** Average score/change in general functioning - SOFAS

**Adverse events:** Number of people with general adverse effects - Overall incidence of AEs

**Adverse events:** Average score/change in specific adverse effects - BAS

**Adverse events:** Number of people with specific adverse effects - Akathisia, muscle rigidity, tremor, dizziness, agitation, insomnia, constipation, SGPT increase, palpitation, headache; cardiovascular, blood and urine

**Other:** Use of anti-Parkinsonian drugs/beta-blockers/anxiolytics/hypnotics, mean systolic/diastolic BP, mean heart rate, mean body weight

**Quality** **1.1 The study addresses an appropriate and clearly focused question.:** Well covered

**1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately

**1.3 An adequate concealment method is used.:** Not addressed

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered

**1.5 The treatment and control groups are similar at the start of the trial.:** Well covered

**1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** <20%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :**

Well covered

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not reported adequately

**2.1 How well was the study done to minimise bias?:** ++

| **Study ID** | **KANE2002** |
|---|---|
| **General info** | **Funding source:** Pharmaceutical industry |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** LOCF |
| | **Type of analysis:** ITT - All patients with at least one baseline and post-baseline evaluation |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment 4 |
| | **Raters:** Independent of treatment |
| | **Design:** Multi-centre 36 centres in US |
| | **Number of people screened, excluded & reasons:** 502 enrolled at baseline, 414 randomised, 248 completed the 4-week study period |
| | **Notes about study methods:** Randomisation method not reported |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 68% |
| | **Diagnosis:** Other schizophrenia related [%] Schizoaffective 32% |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:**<br>- If female: non-pregnant, non-lactating and using suitable contraceptive measures<br>- Aged 18-65<br>- Primary DSM-IV diagnosis of schizophrenia or schizoaffective disorder<br>- Patients taking a long-acting antipsychotic underwent a washout period (time required for one treatment cycle + 1 week), unless investigator judged them to be clinically deteriorating in which case they could be enrolled sooner<br>- PANSS Total >=60, and >=4 (moderate) on any two of the items on the Psychotic subscale.<br>- Prior responsiveness to antipsychotics, defined by: previous schizophrenia/schizoaffective diagnosis, not refractory to antipsychotics, and had improvement produced by an antipsychotic agent other than clozapine, and had been an outpatient for at least one 3-month period in past year. |

**Exclusion criteria:**
- Psychiatric disorder other than schizophrenia or schizoaffective disorder
- History of violence
- History of suicidal attempts or ideation
- Clinically significant neurologic abnormality other than TD or EPS
- Psychoactive drug abuse or dependence
- Drug or alcohol abuse
- Treatment with an investigational drug within 4 weeks prior to washout phase
- Any other acute or unstable mental condition.

**Total sample size:** No. randomised 414

**Total sample size:** ITT population - Not reported

**Total sample size:** Safety population 410

**Gender:** % female 30%

**Age:** Mean 38.6 (0.5)

**Setting:** Other - Not reported

**Setting:** Inpatient

**History:**
[Placebo / Aripiprazole 10mg / Aripiprazole 30mg / Haloperidol]
Age at first episode: 22.5 (0.7) / 21.8 (0.8) / 22.1 (0.7) / 22.9 (0.7)
No. previous hospitalisations: 11.1 (1.5) / 8.4 (1.3) / 10.8 (1.8) / 9.8 (1.4)

**Baseline stats:**
[Placebo / Aripiprazole 10mg / Aripiprazole 30mg / Haloperidol]
PANSS Total: 100.2 (1.6) / 98.5 (1.7) / 99.0 (1.9) / 99.3 (1.7)

**Notes about participants:** Previous antipsychotic use reported in detail

**Interventions**

**Intervention - group 1.:** Placebo; n=106

**Intervention - group 2.:** Aripiprazole 15mg; n=102

**Intervention - group 3.:** Aripiprazole 30mg; n=102

**Intervention - group 4.:** Haloperidol 10mg; n=104

**Notes about the interventions:** Use of psychotropic medications other than the study medication was prohibited throughout the washout and treatment periods, except lorazepam for anxiety or insomnia, or IM for emerging agitation. Benzotropine treatment was allowed for EPS if judged necessary, limited to max 6mg/day.

**Outcomes**

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

| | |
|---|---|
| | **Leaving the study early:** Leaving because of adverse effects |
| | **Global state & service outcomes (e.g. CGI):** Clinically significant response in global state - Response defined as CGI-I score of 1 or 2 at endpoint, or >=30% decrease from baseline in PANSS Total score |
| | **Global state & service outcomes (e.g. CGI):** Average score/change in global state - CGI-Severity, CGI-Improvement |
| | **Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS, PANSS-derived BPRS score |
| | **Adverse events:** Number of people with general adverse effects |
| | **Adverse events:** Number of people with specific adverse effects- List of various AEs, number of people with serious AEs |
| | **Adverse events:** Average score/change in specific adverse effects - SAS, BAS, AIMS |
| | **Other:** Body weight, serum prolactin, QTc interval, vital signs and laboratory analyses |
| **Quality** | **1.1 The study addresses an appropriate and clearly focused question.:** Well covered |
| | **1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately |
| | **1.3 An adequate concealment method is used.:** Not addressed |
| | **1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered |
| | **1.5 The treatment and control groups are similar at the start of the trial.:** Well covered |
| | **1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed |
| | **1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered |
| | **1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** 20-50% |
| | **1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Well covered |
| | **1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not addressed |
| | **2.1 How well was the study done to minimise bias?: +** |

| | |
|---|---|
| **StudyID** | **KANE2007A** |
| **General info** | **Funding source:** Pharmaceutical industry |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** ITT - All those who had received at least one dose of study medication and had a least one post-baseline efficacy |

assessment.

**Blindness:** Double-blind

**Duration:** No. weeks of treatment 6

**Raters:** Not stated to be independent of treatment

**Design:** Multi-centre - 47 centres in Europe and 6 centres in India

**Number of people screened, excluded & reasons:** 680 were screened, 50 were defined as screen failures.

**Notes about study methods:** Randomisation was based on a computer-generated randomisation and stratification scheme. The randomisation was balanced by using permuted blocks of treatments and was stratified by study centre.

**Participants**

**Diagnosis:** Schizophrenia [% of sample] 100%

**Diagnostic tool:** DSM-IV

**Inclusion criteria:**
- diagnosed with schizophrenia according to DSM criteria for >=1 year prior to screening
- agreed to voluntary hospitalisation for a minimum of 14 days during the study
-age >=18 years
- experiencing an acute episode of schizophrenia as represented by a PANSS total score between 70 and 120

**Exclusion criteria:**
- diagnosis of substance dependence within the previous 6 months
- medical condition that could affect absorption, metabolism or excretion of the study drug
- history of tardive dyskinesia or neuroleptic malignant syndrome
- being at significant risk of suicide or violent behaviour
- female participants who were pregnant or breast feeding
- patients receiving a depot antipsychotic within 120 days or paliperidone palmitate as part of a clinical trial within 10 months prior to screening
- use of antidepressants (unless on a stable dose for 3 months prior to study) or mood stabilisers within 2 weeks prior to screening.
- history of drug sensitivity or allergy, including hypersensitivity to risperidone, paliperidone or olanzapine, or a history of unresponsiveness to antipsychotics.

**Total sample size:** No. randomised 630

**Total sample size:** Safety population 629

**Total sample size:** ITT population 628

**Gender:** % female 48%

**Age:** Mean 37.1(10.9)

**Ethnicity:** White - 86%

Asian - <1%
Other - 14%

**Setting:** Inpatient Participants were required to voluntarily admit themselves for at least the first 14 days of the study

**History:**
[Placebo / Paliperidone 6mg / 9mg / 12mg / Olanzapine 10mg]
Age at diagnosis: 28.0(10.2) / 26.1(8.4) / 27.9(8.4) / 26.5(8.8) / 26.5(8.0)
Number of previous hospitalisations (%)
None: 17 / 11 / 12 / 12 / 14
One: 18 / 20 / 9 / 20 / 20
Two: 13 / 17 / 14 / 18 / 16
Three: 11 / 11 / 18 / 12/ 9
>=four: 41 / 41 / 47 / 39 / 41

**Baseline stats:**
[Placebo / Paliperidone 6mg / 9mg / 12mg / Olanzapine 10mg]
PANSS total: 94.1(10.7) / 94.3(10.5) / 93.2(11.9) / 94.6(11.0) / 93.0(10.7)

**Notes about participants:**
[Placebo / Paliperidone 6mg / 9mg / 12mg / Olanzapine 10mg]
Previous antipsychotic therapy, %
Atypical: 61 / 65 / 61 / 60 / 59
Conventional: 61 / 57 / 55 / 56 / 59

**Interventions**

**Intervention - group 1.:** Paliperidone, 6mg/day; n=123

**Intervention - group 2.:** Paliperidone, 9mg/day; n=122

**Intervention - group 3.:** Paliperidone, 12mg/day; n=130

**Intervention - group 4.:** Placebo; n=127

**Intervention group 5:** Olanzapine, 10mg, n=128

**Notes about the interventions:**
The trial started with a 5-day screening period, whereby patients who met inclusion criteria discontinued previous medications 3 days prior to randomisation. These included antipsychotics, antiparkinsonian drugs, beta-blockers and prescription, herbal, or over-the-counter psychotropics.
- Permitted rescue medication included predefined doses of benzodiazepines
- All treatments were fixed oral doses.
- The olanzapine treatment group was not included in the statistical analyses of efficacy assessments if paliperidone was significantly different from placebo in the primary efficacy endpoint.

- Patients were hospitalised from the first day of the double-blind phase for a minimum of 14 days.

**Outcomes**

**Death:** Suicide

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Leaving the study early:** Leaving because of adverse effects

**Global state & service outcomes (e.g. CGI):** Clinically significant response in global state - % classified as 'marked' or 'severely ill'

**Mental state (e.g. BPRS, PANSS, BDI):** Clinically significant response in mental state - Response defined as a >=30% decrease in PANSS total score

Also looked at % with >=50% reduction in PANSS

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS

**General and psychosocial functioning (e.g. SFS):** Clinically significant response in general functioning - % demonstrating an improvement of >=1 category (classified as one 10-point interval)

**General and psychosocial functioning (e.g. SFS):** Average score/change in general functioning - Personal and Social Functioning Scale (PSP)

**Adverse events:** Number of people with specific adverse effects Psychiatric disorders, central and peripheral nervous system disorders, heart rate and rhythm disorders, gastro-intestinal system disorders and cardiovascular disorders.

**Adverse events:** Number of people with general adverse effects

**Adverse events:** Average score/change in specific adverse effects- AIMS; SAS; BARS

**Other:** Weight change, laboratory measures, vital signs, ECG

**Quality**

**1.1 The study addresses an appropriate and clearly focused question.:** Well covered

**1.2 The assignment of subjects to treatment groups is randomised.:** Well covered

**1.3 An adequate concealment method is used.:** Adequately addressed

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered

**1.5 The treatment and control groups are similar at the start of the trial.:** Well covered

**1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** 20-50%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Well covered

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not addressed

**2.1 How well was the study done to minimise bias?: +**

| | |
|---|---|
| **Study ID** | **KASPER2003** |
| **General info** | **Funding source:** Pharmaceutical industry |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** ITT - All participants with at least one post-randomisation assessment |
| | **Type of analysis:** LOCF |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment - 52 |
| | **Raters:** Not stated to be independent of treatment |
| | **Design:** Multi-centre Study 1: 33 centres in the USA<br>Study 2: 137 centres worldwide |
| | **Number of people screened, excluded & reasons:** 1294 completed placebo washout period and randomised |
| | **Notes about study methods:** Randomisation procedures not reported |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 100% |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:**<br>- Age 18-65<br>- DSM-IV schizophrenia<br>- Experiencing acute relapse<br>- History of previous response to antipsychotics other than clozapine and not considered refractory to typical antipsychotic medication<br>- History of continuous treatment on an outpatient basis for at least one 3-month period during past year<br>- PANSS Total >=60 with any two psychosis items >=4<br>- Medically stable as determined by physical examination, ECG and routine lab testing (including serum chemistry, urine toxicology and pregnancy test) |
| | **Exclusion criteria:**<br>- Suicidal ideation, or considered to be at significant risk of suicide<br>- Initial episode of schizophrenia |

- Psychiatric disorder other than schizophrenia requiring pharmacotherapy
- Any significant neurological condition (other than medication-induced EPS or TD) requiring intermittent or maintenance concomitant treatment
- Considered likely to require prohibited concomitant medication or medication that might interfere with the analysis or metabolism of the study drug
- Meeting DSM-IV criteria for psychoactive substance dependence
- Had participated in a previous aripiprazole study or used an investigational medication within 4 weeks of the screening study visit

**Total sample size:** No. randomised 1294

**Total sample size:** ITT population 1283

**Total sample size:** Safety population 1290

**Gender:** % female 41%

**Age:** Mean 37.1 (SE 0.3)

**Ethnicity:** Not reported

**Setting:** Outpatient

**History:**
[Aripiprazole / Haloperidol]
Age at first episode: 24.9 (8.0) / 25.5 (8.5)
Number of hospitalisations: 5.5 (5.9) / 6.1 (8.1)
Number of weeks since start of current relapse: 3.3 (3.4) / 3.3 (2.9)
Length of treatment (weeks) for current relapse: 1.5 (1.5) / 1.5 (1.3)

**Interventions**

**Intervention - group 1.:** Aripiprazole, 30mg; n=861

**Intervention - group 2.:** Haloperidol, Days 1-3: 5mg, Days 4 onwards: 10mg; n=433

**Notes about the interventions:** Randomisation followed a 5 day placebo washout period. During double-blind phase, a one-time dose reduction was permitted as determined by clinical judgement (20mg for aripiprazole or 7mg for haloperidol).

Concomitant medications: Not permitted, except benzodiazepines for anxiety or insomnia, IM benzodiazepines for emerging agitation, anticholinergics for EPS (double-blind phase only). Benzodiazepines were not to exceed equivalent of 4mg lorazepam daily. Other non-psychotropic medications were administered at the investigator's discretion for conditions that emerged or changed during study participation.

**Outcomes**

**Death:** Natural causes

**Death:** Suicide

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Leaving the study early:** Leaving because of adverse effects

**Global state & service outcomes (e.g. CGI):** Average score/change in global state - CGI-S, CGI-I

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS, MADRS, time to failure to maintain response

**Mental state (e.g. BPRS, PANSS, BDI):** Clinically significant response in mental state Response defined as >=20% decrease in PANSS at any timepoint (compared to baseline), providing: CGI was not 6 or 7, there was no AE of worsening schizophrenia and there was not a score of 5, 6 or 7 in any of the four PANSS psychotic subscale items.

Additional response defined as above, except a 30% decrease was required and it had to be maintained for >=28 days

**Adverse events:** Number of people with general adverse effects

**Adverse events:** Average score/change in general adverse effects - Time to discontinuation due to AEs

**Adverse events:** Number of people with specific adverse effects Deaths, serious adverse events, EPS, receiving anticholinergics

**Other:** Vital signs, weight, BMI, serum prolactin, ECG

**Quality**

**1.1 The study addresses an appropriate and clearly focused question.:** Well covered

**1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately

**1.3 An adequate concealment method is used.:** Not addressed

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered

**1.5 The treatment and control groups are similar at the start of the trial.:** Well covered

**1.6 The only difference between groups is the treatment under investigation.:** Well covered

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** >50%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Well covered

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not reported adequately

**2.1 How well was the study done to minimise bias?: +**

**Study ID**

**KONGSAKON2006**

**General info**

**Funding source:** Pharmaceutical industry

| | |
|---|---|
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** Completer |
| | **Type of analysis:** LOCF |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment 24 |
| | **Raters:** Not stated to be independent of treatment |
| | **Design:** Multi-centre Philippines, Pakistan, Malaysia, Thailand, Singapore |
| | **Number of people screened, excluded & reasons:** 440 screened, 309 eligible, 281 randomised, 5 violated protocol (used additional antipsychotics) and excluded from analysis |
| | **Notes about study methods:** Independent centre in Belgium conducted randomisation, in blocks of four stratified by country |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 100% |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:**<br>- Age 18-65<br>- DSM-IV schizophrenia<br>- BPRS >=18<br>- If female of child-bearing potential, had to use a medically accepted means of contraception<br>- Patients and carers were required to be both reliable and in possession of a sufficient level of understanding to achieve compliance with the protocol. |
| | **Total sample size:** No. randomised 281 |
| | **Total sample size:** ITT population 276 |
| | **Gender:** % female 100% |
| | **Age:** Mean 32 |
| | **Ethnicity:** Country of residence<br>Philippines: n=120<br>Pakistan: n=60<br>Malaysia: n=61<br>Thailand: n=57<br>Singapore: n=11 |
| | **Setting:** Outpatient |

**History:** Not reported

**Baseline stats:** Data not shown, but reported to be not significantly different

**Interventions** **Intervention - group 1.:** Olanzapine, 5-20mg; n=144

**Intervention - group 2.:** Haloperidol, 5-20mg; n=132

**Notes about the interventions:**
Study drugs were administered in 5mg increments (one capsule) starting at 5mg/day. Dosage was flexible provided total daily dose remained within 5-20mg. However, increases were constrained by the requirement to allow 7 days between successive increases, and restricted to patients whose CGI-S score >1. No restrictions were placed on dose decreases in response to AEs.

Concomitant psychotropic medications were prohibited, except for anticholinergics for EPS (not exceeding 6mg/day benzotropine mesylate or biperiden equiv.). Hypnotics were allowed only for sleep, not exceeding 40mg/day diazepam equiv.

**Outcomes** **Leaving the study early:** Leaving because of adverse effects

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Global state & service outcomes (e.g. CGI):** Average score/change in global state - CGI-S

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - BPRS, PANSS

**Adverse events:** Number of people with specific adverse effects - Various

**Adverse events:** Average score/change in specific adverse effects - BAS, AIMS, SAS

**Quality of Life:** Average score/change in quality of life - QLS, WHOQOL-BREF

**Other:** Weight, routine lab tests (electrolyte, blood, etc.), use of concomitant medications

**Quality** **1.2 The assignment of subjects to treatment groups is randomised.:** Well covered

**1.3 An adequate concealment method is used.:** Well covered

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered

**1.5 The treatment and control groups are similar at the start of the trial.:** Adequately addressed

**1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Adequately addressed

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** 20-50%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Not reported adequately

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not reported adequately

**2.1 How well was the study done to minimise bias?: +**

| | |
|---|---|
| **Study ID** | **MARDER2007** |
| **General info** | **Funding source:** Pharmaceutical industry |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** LOCF |
| | **Type of analysis:** ITT patients who received one or more doses of study medication and had one or more post-baseline assessments |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment 6 |
| | **Raters:** Not stated to be independent of treatment |
| | **Design:** Multi-centre 74 centres in the US |
| | **Number of people screened, excluded & reasons:** Not reported |
| | **Notes about study methods:** Computer-generated randomisation and stratification scheme using an Interactive Voice Response System. Randomisation was balanced by using permuted blocks of treatments and stratified by study centre. |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 100% |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:**<br>- >=18 years<br>- DSM-IV diagnosis of schizophrenia for at least 1 year prior to screening and experiencing an acute episode as represented by PANSS total score of 70-120<br>- agree to voluntary hospitalisation for a minimum of 14 days |
| | **Exclusion criteria:**<br>- diagnosis of substance dependence within previous 6 months<br>- medical condition which could affect absorption, metabolism or excretion of study drug<br>- history of tardive dyskinesia or neuroleptic malignant syndrome<br>- significant risk of suicide or violent behaviour<br>- pregnant or breastfeeding female participants<br>- patients receiving a depot antipsychotic within 120 days of screening or paliperidone palmitate as part of a clinical trial within 10 months before screening. |

-a history of drug sensitivity or allergy including hypersensitivity to risperidone, paliperidone, or olanzapine; history of unresponsiveness to antipsychotics.

**Total sample size:** No. randomised 444

**Total sample size:** ITT population 432

**Total sample size:** Safety population 439

**Gender:** % female 26%

**Age:** Mean 41.6

**Ethnicity:** Reported in a supplement not yet available online (article still in press)

**Setting:** Outpatient

**Setting:** Inpatient All patients agreed to a voluntary hospital admission for >=14 days at the beginning of the study

**History:** Reported in a supplement not yet available online (article still in press)

**Baseline stats:**
[Placebo / Paliperidone ER 6mg / 12mg / Olanzapine]
PANSS total: 93.6(11.7) / 92.3(12.0) / 94.1(11.4) / 94.9(12.4)

**Notes about participants:** Reported in a supplement not yet available online (article still in press)

**Interventions**

**Intervention - group 1.:** Paliperidone Extended Release, 6mg/day; n=111

**Intervention - group 2.:** Paliperidone Extended Release, 12mg/day; n=111

**Intervention - group 3.:** Placebo; n=105

**Intervention - group 4.:** Olanzapine, 10mg/day; n=105

**Notes about the interventions:**
During a 5-day screening period, patients included in the study discontinued prior medications, including antipsychotic medication, antiparkinsonian drugs, beta-blockers and prescription, herbal or over-the-counter psychotropics, for 3 days before randomisation.
- Permitted rescue medication included pre-defined doses of benzodiazepine. Antidepressant use was also permitted for patients on a stable dose for 3 months prior to study.
- Participants received fixed doses of 6 or 12mg/day throughout the study
- The Olanzapine group was included to provide a concurrent active control in order to confirm the study was adequate to detect a drug effect in the event of a negative finding for paliperidone. The study was not designed to support comparisons between paliperidone ER and olanzapine.

**Outcomes**

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Global state & service outcomes (e.g. CGI):** Clinically significant response in global state % changing CGI categories

**Global state & service outcomes (e.g. CGI):** Average score/change in global state CGI

**Mental state (e.g. BPRS, PANSS, BDI):** Clinically significant response in mental state - Clinical response defined as >=30% reduction in PANSS total; % with >=50% reduction in PANSS total

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS total and Marder factors

**General and psychosocial functioning (e.g. SFS):** Average score/change in general functioning - PSP

**Adverse events:** Number of people with specific adverse effects table showing all AEs occurring in >=5% of participants.
- Most commonly reported AEs included headache, somnolence, insomnia and dyspepsia

**Adverse events:** Average score/change in specific adverse effects - BAS; SAS; AIMS

**Adverse events:** Number of people with general adverse effects

**Non-adherence to study medication:** Non-adherence - Treatment compliance assessed from an inventory of drug supplies for each patient by used and unused tablets in the blister packs returned to the study centre.

**Other:** % using rescue medications; onset of therapeutic effect; clinical laboratory tests including haematology, fasting serum chemistry including fasting glucose, lipids and prolactin levels; bodyweight; significant bodyweight change; ECG and vital signs.

**Quality**

**1.1 The study addresses an appropriate and clearly focused question.:** Well covered

**1.2 The assignment of subjects to treatment groups is randomised.:** Well covered

**1.3 An adequate concealment method is used.:** Well covered

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered

**1.5 The treatment and control groups are similar at the start of the trial.:** Not reported adequately

**1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** >50% 57% did not complete study

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Adequately addressed

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Well covered

**2.1 How well was the study done to minimise bias?: +**

**Study ID**

**MARTIN2002**

**General info**

**Funding source:** Not mentioned

**Published or unpublished data?:** Published

**Method**

**Type of study:** Individual randomised trial (Noninferiority/equivalence)

**Type of analysis:** ITT Provided at least one post-baseline outcome measure

**Type of analysis:** LOCF

**Blindness:** Double-blind

**Duration:** Mean duration (for each group) Amisulpride: 51 (15) days
Olanzapine: 50 (17) days

**Duration:** No. weeks of treatment 24

**Raters:** Not stated to be independent of treatment

**Design:** Multi-centre 76 centres in Belgium, Switzerland, Denmark, France, Great Britain, Czech Republic, Tunisia, Hungary, Morocco, Portugal

**Number of people screened, excluded & reasons:** Not mentioned

**Notes about study methods:** Randomisation procedures not reported.

**Participants**

**Diagnosis:** Schizophrenia [% of sample] 98%

**Diagnosis:** Other schizophrenia related [%] Schizophreniform 2%

**Diagnostic tool:** DSM-IV

**Inclusion criteria:**
- DSM-IV schizophrenia (paranoid, disorganised or undifferentiated) or schizophreniform disorder
- Aged 18-65
- BPRS >=36, and PANSS Positive > PANSS negative

**Exclusion criteria:**
- BPRS improved by 40% between screening and baseline visit
- Pregnant or lactating
- If female and of child-bearing age, not reporting use of adequate contraception.

**Total sample size:** No. randomised 377

**Total sample size:** ITT population 372

**Gender:** % female 35%

**Age:** Mean 37.8

**Age:**
[Amisulpride / Olanzapine]
Age range: 18-64 / 18-67

**Setting:** Outpatient

**Setting:** Inpatient

**History:**
[Amisulpride / Olanzapine]
Years of illness: 9.56 (9.50) / 8.12 (8.79)
Inpatient: 56.1% / 57.4%

**Baseline stats:**
[Amisulpride / Olanzapine]
BPRS: 56.0 (9.8) / 55.1 (9.7)
PANSS Positive: 26.5 (5.0) / 26.2 (5.6)
PANSS Negative: 19.9 (4.6) / 20.4 (4.8)
PANSS Total: 94.0 (15.9) / 93.2 (16.0)
MADRS: 16.6 (7.9) / 16.6 (7.5)

**Notes about participants:** Medication: Three day washout period (or one injection interval for those on depots) prior to baseline visit. Concomitant benzodiazepine use was allowed >=2 weeks before screening visit.

**Interventions**

**Intervention - group 1.:** Amisulpride: 400mg/day starting dose, titrated to 200-800mg/day over 3 weeks according to individual response; n=189

**Intervention - group 2.:** Olanzapine: 10mg/day starting dose, titrated to 5-20mg/day over 3 weeks according to individual response; n=188

**Notes about the interventions:** Blinding ensured by supplying medications in opaque green capsules, and in two different blister backs for high and low dosages for each medication (200mg amisulpride/5mg olanzapine, 400mg amisulpride/10mg olanzapine), which could be combined in different permutations at investigator's discretion whilst still maintaining blindness to medication.

**Outcomes**

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Leaving the study early:** Leaving because of adverse effects

**Global state & service outcomes (e.g. CGI):** Re-hospitalisation

**Global state & service outcomes (e.g. CGI):** Clinically significant response in global state - CGI: response defined as very much or much improved on Item 2 of the scale

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - BPRS, PANSS, MADRS

**Mental state (e.g. BPRS, PANSS, BDI):** Clinically significant response in mental state - MADRS: 'response' defined as >=50% decrease from baseline, 'remission' as final score <=10.

**Adverse events:** Average score/change in specific adverse effects Simpson Angus Scale

**Other:** BMI, body weight, 'clinically relevant change' in body weight (defined as >=7% increase)

**Quality**

**1.1 The study addresses an appropriate and clearly focused question.:** Adequately addressed

**1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately

**1.3 An adequate concealment method is used.:** Not addressed

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered

**1.5 The treatment and control groups are similar at the start of the trial.:** Well covered

**1.6 The only difference between groups is the treatment under investigation.:** Not addressed

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** 20-50%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Well covered

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not addressed

**2.1 How well was the study done to minimise bias?: +**

| **Study ID** | **POTKIN2003A** |
|---|---|
| **General info** | **Funding source:** Pharmaceutical industry |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** ITT - All randomised with at least one post-randomisation evaluation |
| | **Type of analysis:** LOCF |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment 4 |
| | **Raters:** Not stated to be independent of treatment |
| | **Design:** Multi-centre 40 centres in the US |
| | **Number of people screened, excluded & reasons:** 487 screened, 448 underwent placebo washout, 404 randomised |
| | **Notes about study methods:** Randomisation procedures not reported |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 72% |
| | **Diagnosis:** Other schizophrenia related [%] Schizoaffective 28% |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:** |

- Age 18-65
- Primary DSM-IV diagnosis of schizophrenia or schizoaffective disorder
- Hospitalised due to an acute relapse
- Evidence for responsiveness to antipsychotics (i.e. not refractory to antipsychotics, had shown previous improvement with an antipsychotic other than clozapine, and had been an outpatient for at least one 3-month period in past year)
- PANSS total >=60, and >=4 on at least two items from the Psychotic subscale
- If taking a long-acting antipsychotic, at least 1 treatment cycle plus 1 week must have elapsed since last treatment or judged to be clinically deteriorating.

**Exclusion criteria:**
- Psychiatric disorder other than schizophrenia or schizoaffective disorder requiring pharmacotherapy
- History of violence
- Recent history of suicide attempts or ideation
- Clinically significant neurological abnormality other than TD or EPS
- Current diagnosis of psychoactive substance dependence, or history of drug or alcohol abuse (DSM-IV) in past month
- Treatment with a investigational drug in the 4 weeks prior to the washout phase
- Any other acute or unstable medical condition.

**Total sample size:** No. randomised 404

**Total sample size:** ITT population 392

**Total sample size:** Safety population 403

**Gender:** % female 30%

**Age:** Mean 38.9

**Ethnicity:** No mention

**Setting:** Inpatient

**History:** No. of hospitalisations: 8.6

**Baseline stats:**
[Placebo / Ari 20mg / Ari 30mg / Ris 6mg]
PANSS: 95.7 / 94.4 / 92.6 / 94.9
CGI-S: 4.8 / 4.8 / 4.8 /4.8

**Notes about participants:** All eligible participants underwent a minimum 5-day placebo washout period starting within 1 week of screening visit.

**Interventions** **Intervention - group 1.:** Aripiprazole, 20mg/day ; n=103

**Intervention - group 2.:** Aripiprazole, 30mg/d ; n=101

| | |
|---|---|
| | **Intervention - group 3.:** Risperidone, 6mg/d; n=99 |
| | **Intervention - group 4.:** Placebo; n=103 |
| **Quality** | **1.1 The study addresses an appropriate and clearly focused question.:** Well covered |
| | **1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately |
| | **1.3 An adequate concealment method is used.:** Not addressed |
| | **1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered |
| | **1.6 The only difference between groups is the treatment under investigation.:** Well covered |
| | **1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered |
| | **1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** 20-50% |
| | **1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Well covered |
| | **1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Well covered |
| | **2.1 How well was the study done to minimise bias?: +** |

| | |
|---|---|
| **Study ID** | **RIEDEL2007B** |
| **General info** | **Funding source:** Not mentioned |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** LOCF |
| | **Type of analysis:** ITT - those who completed cognitive assessments at least at two or more time points out of three (baseline, week 4 and week 8) |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment 8 |
| | **Raters:** Not stated to be independent of treatment |
| | **Number of people screened, excluded & reasons:** Not reported |
| | **Notes about study methods:** Randomisation procedure not reported |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 100% |

**Diagnostic tool:** DSM-IV

**Inclusion criteria:**
- Inpatients aged 18-65
- CGI >4; PANSS >60

**Exclusion criteria:**
- substance abuse, dependence or intoxication, suicidal tendencies,
- significant medical history (head trauma, epilepsy, meningo-encephalitis), ECG or EEG abnormalities; laboratory testing (blood and urine) >20% different from reference ranges,
- pregnancy or lactation
- treatment with clozapine within 4 weeks of enrolment

**Total sample size:** No. randomised 52

**Total sample size:** ITT population 33

**Gender:** % female 36%

**Age:** Mean 35

**Setting:** Inpatient

**History:**
[Quetiapine / Olanzapine]
Age of onset: 25.25(7.10) / 29.76(9.00)
Duration of illness: 8.44(10.11) / 4.71(6.22)

**Baseline stats:**
[Quetiapine / Olanzapine]
PANSS: 100.31(13.93) / 90.06(20.79)
CGI: 5.63(0.62) / 5.35(0.70)
ESRS: 0.25(1.00) / 1.00(2.48)
BAS: 0.00(0.00) / 0.35(1.46)
UKU: 1.44(4.50) / 0.06(0.20)
MWT-B: 26.56(7.99) / 25.06(8.00)

**Notes about participants:**
- Prior to inclusion: 21 participants - antipsychotically untreated at least for 4 weeks, 8 - treated with conventional antipsychotics, 7 - treated with atypical antipsychotics

**Interventions**

**Intervention - group 1.:** Olanzapine, 10-20 mg/day; n=17 (number of completers; number randomised not reported)

**Intervention - group 2.:** Quetiapine, 400-800mg/day; n=16 (number of completers; number randomised not reported)

**Notes about the interventions:**

2-7 day washout period prior to study inclusion.

Quetiapine:
initiated at 50mg on day 1 and titrated up to 600mg/day within the first 7 days. Thereafter, dosage was flexible between 400-800mg/day depending on clinician's judgment.
- mean dose = 586.86(169.12) mg/day

Olanzapine:
initiated at 10mg on day 1 and titrated up to 15mg/day within the first 7 days. Thereafter, dosage was flexible between 10-20 mg/day depending on clinician's judgment.
- mean dose = 15.82(5.44) mg/day

-During the trial anticholinergic medication was administered. Concomitant lorazepam and zopiclone were also permitted but had to be discontinued 24h prior to neurocognitive testing.

**Outcomes**

**Leaving the study early:** Leaving because of adverse effects

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Global state & service outcomes (e.g. CGI):** Average score/change in global state - CGI

**Global state & service outcomes (e.g. CGI):** Clinically significant response in global state - CGI - % changing from "markedly ill" to "moderately ill"

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS

**Adverse events:** Average score/change in specific adverse effects - ESRS; BAS; UKU

**Adverse events:** Number of people with general adverse effects

**Adverse events:** Number of people with specific adverse effects

**Cognitive functioning:** Average score/change in cognitive functioning - Neurocognitive battery of tests administered assessing the following domains: Working memory; verbal memory; reaction time; reaction quality/attention; executive function, and visual memory

**Other:** body weight

**Quality**

**1.1 The study addresses an appropriate and clearly focused question.:** Adequately addressed

**1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately

**1.3 An adequate concealment method is used.:** Not addressed

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered

**1.5 The treatment and control groups are similar at the start of the trial.:** Adequately addressed

**1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** 20-50% 37%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Poorly addressed Only completers were analysed and number randomised to each group was not reported.

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not applicable

**2.1 How well was the study done to minimise bias?: +**

| **Study ID** | **ROSENHECK2003** |
|---|---|
| **General info** | **Funding source:** Pharmaceutical industry |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial (effectiveness/pragmatic) |
| | **Type of analysis:** ITT All patients as randomised |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment 52 |
| | **Raters:** Not stated to be independent of treatment |
| | **Design:** Multi-centre 17 Department of Veteran Affairs centres across US |
| | **Number of people screened, excluded & reasons:** 4386 records reviewed, 2141 eligible for further assessment, 1530 patients or their clinicians refused consent, 302 could not participate for other reasons<br><br>309 provided consent and randomised<br><br>Data from one site were excluded due to problems with local institution review board unrelated to this study. |
| | **Notes about study methods:** Randomisation: Medication kits were prepared in a set of 4 and each was labelled with a random sequence number. Patients were assigned a kit at the end of a telephone conversation with the coordinating centre. |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 100% (or schizoaffective) |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:**<br>- DSM-IV schizophrenia or schizoaffective disorder diagnosis |

- BPRS >=36
- Current or history of psychiatric hospitalisation in past 2 years
- Serious dysfunction for past 2 years with inability to work or social constriction

**Exclusion criteria:**
- Patient or clinician unable or unwilling to cooperate
- Serious medical illness
- Unexplained seizures
- Severe medication allergies
- Previous participation in olanzapine research

**Total sample size:** No. randomised 309

**Total sample size:** ITT population 309

**Gender:** % female 4%

**Age:**
Olanzapine: 46.8 (9.5)
Haloperidol: 46.2 (7.7)

**Ethnicity:**
[Olanzapine / Haloperidol]
White: 42% / 39%
African American: 52% / 51%
Hispanic: 5% / 9%
Other: 2% / 1%

**Setting:** Outpatient

**Setting:** Inpatient

**History:**
[Olanzapine / Haloperidol]
Age of onset: 23.7 (4.9) / 24.4 (5.9)

**Baseline stats:**
[Olanzapine / Haloperidol]
Lifetime comorbidity
Major depressive episode: 14% / 17%
Alcohol misuse or dependence: 56% / 65%
Drug misuse: 43% / 49%
Cocaine abuse: 30% / 35%

Alcohol or drug abuse in past 6mths: 17% / 25%

BPRS Total: 49.7 (8.6) / 48.7 (8.5)
PANSS Total: 87.5 (15.4) / 85.2 (15.5)
AIMS: 5.0 (5.5) / 5.2 (5.9)
SAS: 0.4 (0.4) / 0.4 (0.4)
BAS: 0.8 (1.0) / 0.8 (1.0)
CGI: 4.5 (0.8) / 4.5 (0.7)

**Interventions**

**Intervention - group 1.:** Olanzapine, 5-20mg/day; n=159

**Intervention - group 2.:** Haloperidol 5-20mg/day; n=150

**Notes about the interventions:**
Dose adjustments were made as clinically indicated using 4 fixed dosage levels at 5mg intervals

Patients assigned to haloperidol also received prophylactic benztropine mesylate (1-4mg/d) for EPS. Olanzapine group received matching placebo benztropine.

Concomitant antipsychotic medications were not allowed, but other psychotropic medications were allowed.

A predefined programme of psychosocial treatment was offered to both groups through a structured treatment process.

**Outcomes**

**Leaving the study early:** Leaving because of adverse effects

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Global state & service outcomes (e.g. CGI):** Average score/change in global state - SF-36

**Mental state (e.g. BPRS, PANSS, BDI):** Clinically significant response in mental state Response as 20% improvement in PANSS

**Adverse events:** Average score/change in specific adverse effects - SAS, AIMS, BAS - no appropriate data

**Adverse events:** Number of people with specific adverse effects weight gain, restlessness - Akathisia - no appropriate data

**Engagement with services (e.g. SES):** Average score/change in engagement with services Use of services: outpatient (visits) and inpatient/residential (days)

**Quality of Life:** Average score/change in quality of life - QOLS

**Cognitive functioning:** Average score/change in cognitive functioning - Cognitive functioning, motor functioning, WCST

**Other:** Use of other medications - where appropriate

**Quality**

**1.1 The study addresses an appropriate and clearly focused question.:** Well covered

**1.2 The assignment of subjects to treatment groups is randomised.:** Adequately addressed

**1.3 An adequate concealment method is used.:** Adequately addressed

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered

**1.5 The treatment and control groups are similar at the start of the trial.:** Well covered

**1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** >50%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Well covered

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not reported adequately

**2.1 How well was the study done to minimise bias?: ++**

| **Study ID** | **STUDY-S036** |
|---|---|
| **General info** | **Funding source:** Pharmaceutical industry |
| | **Published or unpublished data?:** Unpublished |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** LOCF |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment 6 with an optional 2-week extension period |
| | **Raters:** Not stated to be independent of treatment |
| | **Design:** Multi-centre- 5 centres in 1 country |
| | **Number of people screened, excluded & reasons:** 123 participants were screened of which 122 were randomised - no further details reported |
| | **Notes about study methods:** Method of randomisation not reported |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] % not reported |
| | **Diagnosis:** Other schizophrenia related [%] Schizoaffective disorder - % not reported<br>Schizophreniform - % not reported |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:** |

- DSM-IV diagnosis of schizophrenia, schizoaffective disorder, or schizophreniform.
- male or female
- aged 18-60

**Total sample size:** No. randomised 122

**Total sample size:** ITT population - Not reported
102 completed study

**Gender:** % female 56%

**Age:** Mean 33

**Ethnicity:**
Han - 98.5%
Hui - 1.5%

**Setting:** Inpatient

**History:**
[Olanzapine / Risperidone]
Age of first episode: 27.8 / 26.6
Duration of present episode (months): 12.3 / 7.5

**Baseline stats:**
[Olanzapine / Risperidone]
BPRS: 52.1(7.9) / 53.3(9.4)
PANSS: 48.8(20.1) / 48.4(18.7)

**Interventions**

**Intervention - group 1.:** Olanzapine, max dose - 20mg/d; n=63

**Intervention - group 2.:** Risperidone, max dose 6mg/d; n=59

**Notes about the interventions:**
Rapid Initial dose phase occurred for both drugs during days 1-3

Olanzapine:
- Rapid Initial Dose Phase (Days 1 to 3): if the initial dose was 10 or 15 mg, a second dose of 10 or 5 mg was allowed ≥ 6 hours after initial dose and following completion of the 6-hour, post-dose measures. Maximum daily dose was
20 mg.
- Usual Dose Treatment Phase Days 4 through 7: 10 to 20 mg once per day; weeks 2 through 6: 5 to 20 mg once per day.

Risperidone:
- Rapid Initial Dose Phase (Days 1 through 3): after the initial 1-mg dose, a second dose of 1 mg was allowed ≥ 6 hours after initial dose and

following completion of the 6-hour, post-dose measures. Maximum daily dose was 2 mg.
- Usual Dose Treatment Phase Days 4 through 7: titration was allowed to between 1 and 3 mg per day. Maximum daily dose was 3 mg; weeks 2 through 6: titration was allowed to between 2 to 6 mg per day.

**Outcomes**

**Death:** Suicide

**Death:** Natural causes

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Global state & service outcomes (e.g. CGI):** Average score/change in global state - CGI-S; CGI-I

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - BPRS; PANSS; ACES

**Mental state (e.g. BPRS, PANSS, BDI):** Clinically significant response in mental state Response defined as >=40% reduction from baseline

**Adverse events:** Number of people with general adverse effects

**Adverse events:** Number of people with specific adverse effects - Reports number of participants with >=1 AES and all AEs reported

**Adverse events:** Average score/change in specific adverse effects - BAS; SAS

**Quality**

**1.1 The study addresses an appropriate and clearly focused question.:** Adequately addressed

**1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately Study summary only

**1.3 An adequate concealment method is used.:** Not addressed

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered

**1.5 The treatment and control groups are similar at the start of the trial.:** Adequately addressed

**1.6 The only difference between groups is the treatment under investigation.:** Not reported adequately Study summary only

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** <20%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Adequately addressed

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not addressed

**2.1 How well was the study done to minimise bias?: +**

| Study ID | WAGNER2005 |
|---|---|
| General info | **Funding source:** Pharmaceutical industry |
| | **Published or unpublished data?:** Published |
| Method | **Type of study:** Individual randomised trial |
| | **Type of analysis:** ITT Sample with neuropsychological data at least for weeks 1 and 4 |
| | **Type of analysis:** LOCF |
| | **Blindness:** Double-blind |
| | **Duration:** Mean duration (for each group)<br>[Amisulpride / Olanzapine]<br>Mean weeks in study: 7.3(1.3) / 6.9(1.8) |
| | **Duration:** No. weeks of treatment 8 |
| | **Raters:** Independent of treatment |
| | **Design:** Single-centre - Germany |
| | **Number of people screened, excluded & reasons:** Not reported |
| | **Notes about study methods:** Randomisation was performed by distributing the study medications to containers according to a pseudo-random computer algorithm |
| Participants | **Diagnosis:** Schizophrenia [% of sample] 100% |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:**<br>- Admitted for in-patient treatment with a diagnosis of Schizophrenia<br>- Aged 18-65<br>- CGI =>4; PANSS =>61<br>-No Clozapine treatment within 3 months prior to study |
| | **Exclusion criteria:**<br>- History of CNS trauma, epilepsy, meningoencephalitis, instable somatic condition, substance dependency<br>- Lack of sufficient contraception in premenopausal females.<br>- History of antipsychotic drug resistance, risk of suicide or aggressive behaviour. |
| | **Total sample size:** No. randomised 52 |
| | **Total sample size:** ITT population 36 |
| | **Gender:** % female 36 |

**Age:** Mean 36.3

**Setting:** Inpatient

**History:**
[Amisulpride / Olanzapine]
Age of onset: 28.4(7.6) / 27.3(7.0)
Duration of illness (yrs): 9.8(11.2) / 7.0(6.7)
Number of episodes: 3.1(1.7) / 2.8(2.4)

**Baseline stats:** Details of scores at inclusion to study are reported only in graph format. Numerical values are not reported for inclusion but are reported at week 1.

[Amisulpride / Olanzapine]
Global Cognitive Index*: 0.06(0.47) / -0.06(0.72)
Neurocognitive domain scores*:
Attention: -0.05(0.53) / 0.05(0.67)
Executive functions: 0.02(0.56) / -0.02(0.76)
Working memory: 0.14(0.62) / -0.14(0.99)
Declarative memory: 0.11(0.62) / -0.11(0.85)

*A total of 17 variables were extracted from the neuropsychological tests for each test session. The neuropsychological data was standardized with reference to the mean and standard deviation of the entire sample(negative values reflect impairment). The common z-metric allows for an integration of single variables into cognitive domains and into a global cognitive index, which were the primary study outcomes.

**Notes about participants:**
- Wash-out phase of 2 days, in which only lorazepam up to 4mg daily was permitted.
The following pharmacological treatments were permitted:
-up to 4mg/day lorazepam
-zopiclone up to 22.5 mg/day
-up to 4mg/day of biperiden

All were tapered 24h before testing

**Interventions**

**Intervention - group 1.:** Amisulpride
- started with 400mg/day for day 1. According to clinical response, the dosage was adjusted within 3 days between 400-800mg/day.
-mean end dose = 511.1(171.1)mg/day
- n=26 (ITT pop n=18)

**Intervention - group 2.:** Olanzapine

- Started at 10mg/day. According to clinical response, the dosage was varied within the first 3 days between 10-20mg/day.
-mean end dose = 15.0(4.5) mg/day
-n=26 (ITT pop n=18)

**Notes about the interventions:** Blinding method not reported

**Outcomes**

**Leaving the study early:** Leaving because of adverse effects

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Global state & service outcomes (e.g. CGI):** Average score/change in global state - CGI

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS; SANS

**Adverse events:** Number of people with general adverse effects

**Adverse events:** Average score/change in specific adverse effects - SAS

**Adverse events:** Number of people with specific adverse effects

**Cognitive functioning:** Average score/change in cognitive functioning: A z-score based on the outcome of 17 different tests was calculated for each of the following cognitive domains: attention; executive functions; working memory, and declarative memory.

**Quality**

**1.1 The study addresses an appropriate and clearly focused question.:** Adequately addressed

**1.3 An adequate concealment method is used.:** Not addressed

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered

**1.5 The treatment and control groups are similar at the start of the trial.:** Adequately addressed

**1.6 The only difference between groups is the treatment under investigation.:** Not addressed

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Adequately addressed

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not applicable

**2.1 How well was the study done to minimise bias?: +**

**Study ID**

**ZHANG2001**

**General info**

**Funding source:** Not mentioned

**Published or unpublished data?:** Published

**Method**

**Type of study:** Individual randomised trial

**Type of analysis:** Completer

**Type of analysis:** ITT - Dropouts were included in the ITT analysis for clinical response, but not for other efficacy measures

**Blindness:** Double-blind

**Duration:** No. weeks of treatment 12 weeks

**Raters:** Not stated to be independent of treatment

**Design:** Single-centre - Psychiatric hospital in Beijing City

**Number of people screened, excluded & reasons:** 80 enrolled, 78 completed placebo washout phase and randomised

**Participants**

**Total sample size:** No. randomised 78

**Total sample size:** ITT population 70

**Gender:** % female 20%

**Age:** Mean 44

**Ethnicity:** Chinese

**Setting:** Inpatient

**History:** Years of illness
Risperidone: 21.6 (10.9)
Haloperidol: 19.2 (9.4)

**Baseline stats:** CGI-S
Risperidone: 5.8 (1.2)
Haloperidol: 5.7 (1.1)

**Interventions**

**Intervention - group 1.:** Risperidone, 6mg/day; n=41

**Intervention - group 2.:** Haloperidol, 20mg/day; n=37

**Notes about the interventions:** Concomitant medications included choral hydrate or lorazepam for insomnia or sedation, and benzhexol hydrochloride as anti-parkinsonian agents for extrapyramidal symptoms as determined by blinded psychiatrists. No other concomitant psychotropic medications were allowed.

**Outcomes**

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state PANSS

**Mental state (e.g. BPRS, PANSS, BDI):** Clinically significant response in mental state - Response/improvement defined as >=20% decrease in PANSS, using a modification of Kane et al. (1998) criteria.
'Much improved' defined as 50-70% decrease in PANSS
'Very much improved' defined as >=70% decrease.

**Adverse events:** Average score/change in specific adverse effects Use of benzhexol hydrochloride

| | |
|---|---|
| | **Adverse events:** Average score/change in general adverse effects TESS |
| | **Adverse events:** Number of people with specific adverse effects Use of antiparkinsonian medication |
| **Quality** | **1.1 The study addresses an appropriate and clearly focused question.:** Well covered |
| | **1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately |
| | **1.3 An adequate concealment method is used.:** Not addressed |
| | **1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered |
| | **1.5 The treatment and control groups are similar at the start of the trial.:** Well covered |
| | **1.6 The only difference between groups is the treatment under investigation.:** Well covered |
| | **1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered |
| | **1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** <20% |
| | **1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Adequately addressed |
| | **1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not applicable |
| | **2.1 How well was the study done to minimise bias?: +** |

| | |
|---|---|
| **Study ID** | **ZHONG2006** |
| **General info** | **Funding source:** Pharmaceutical industry |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial (Noninferiority/equivalence) |
| | **Type of analysis:** Completer |
| | **Type of analysis:** LOCF |
| | **Type of analysis:** Observed case |
| | **Type of analysis:** Modified ITT - all those randomly assigned to treatment, received at least 1 dose of study medication, and had at least 1 post-baseline assessment. |
| | **Blindness:** Double-blind |
| | **Duration:** Mean duration (for each group) approx. 5 weeks for both quetiapine and risperidone (34.7 and 36.5 days respectively) |
| | **Duration:** No. weeks of treatment 8 |

**Raters:** Not stated to be independent of treatment

**Design:** Multi-centre - 66 centres in the United States.

**Number of people screened, excluded & reasons:** screened = 872,
excluded = 199
Reasons not stated

**Notes about study methods:** Randomisation procedure not reported.

**Participants**

**Diagnosis:** Schizophrenia [% of sample] 100%

**Diagnostic tool:** DSM-IV

**Inclusion criteria:**
- aged 18-65
- PANSS >= 60; Score of >=4 on 1 or more of following PANSS items: delusions, conceptual disorganisation, hallucinations, suspiciousness, or persecution.
- CGI >=4, with evidence of clinical deterioration in the preceding 3 weeks preceding randomisation.

**Exclusion criteria:**
- DSM-IV Axis I disorder other than schizophrenia (including schizoaffective disorder); psychotic illness due to a general medical condition, mental retardation.
- known intolerance or lack of response to previous treatment with quetiapine or risperidone.
- use of chlorapine within 1 month of randomisation, use of prohibited medications.
- pregnancy, lactation or failure to use reliable contraception.

**Total sample size:** No. randomised 673

**Total sample size:** ITT population; MITT = 648

**Total sample size:** Safety population 672

**Gender:** % female 24%

**Age:** Mean 40

**Ethnicity:** African American = 50%
White = 39%
Hispanic = 7%
Other = 4%

**History:** Age of onset and duration of illness not reported

**Baseline stats:**
[Quetiapine / Risperidone]
PANSS: 92.9(19.7) / 92.1(17.5)

CGI: 4.6(0.7) / 4.6(0.7)

**Notes about participants:**
[Quetiapine / Risperidone]
Previous medication (%): 96.4 / 95.2
Olanzapine: 36.1 / 40.3
Risperidone: 29.3 / 27.5
Haloperidol: 16.3 / 18.8
Quetiapine: 13.3 / 9.9
Ziprasidone: 8.0 / 4.2
Chlorpromazine: 2.4 / 2.4
Loxapine: 0.9 / 1.2
Clozapine: 0.6 / 0
Molindone: 0 / 0.3

Antipsychotics, anxiolytics, mood stabilisers, and potent cytochrome 450 inducers and inhibitors were prohibited during trial

Anticholinergics permitted only for treatment of EPS.

Lorazepam permitted for agitation up to and not beyond day 3 of the study.

**Interventions**

**Intervention - group 1.:** Quetiapine
- day 1 = 50mg/day, day 2 = 100mg/day, after which the daily dose was titrated in 100mg increments up to 400mg/day on day 5. Thereafter, investigators could adjust the dose according to patient's response and tolerability between 200 - 800 mg/day.
- mean modal dose = 525(231) mg/day
- n=338 (n=328 ITT population)

**Intervention - group 2.:** Risperidone:
- Day 1 = 2mg/day, Day 3&4 = 3mg/day, Day 5 = 4mg/day. Thereafter, investigators could adjust the doses according to clinical response and tolerability between 2-8mg/day.
- Mean modal dose = 6.0(1.8) mg/day
- n=335 (n=320 ITT population)

**Notes about the interventions:** Study medication administered orally as identical encapsulated tablets twice daily throughout the randomised period.

**Outcomes**

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Leaving the study early:** Leaving because of adverse effects

| | |
|---|---|
| | **Global state & service outcomes (e.g. CGI):** Clinically significant response in global state - CGI - % rated as "much" or "very much" improved |
| | **Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS |
| | **Mental state (e.g. BPRS, PANSS, BDI):** Clinically significant response in mental state - PANSS: % achieved a => 30% and =>40% reduction |
| | **General and psychosocial functioning (e.g. SFS):** Average score/change in general functioning measures of social functioning - Penn Emotional Acuity Test (PEAT); Social Skills Performance Assessment (SSPA) |
| | **Adverse events:** Number of people with general adverse effects |
| | **Adverse events:** Average score/change in specific adverse effects- AIMS; BARS; SAS |
| | **Adverse events:** Number of people with specific adverse effects |
| | **Cognitive functioning:** Average score/change in cognitive functioning - phonological fluency; CPT; TMT-A; TMT-B; Ray verbal learning test |
| | **Other:** Clinical laboratory assessments: serum prolactin; random serum glucose levels; vital signs; BMI |
| **Quality** | **1.1 The study addresses an appropriate and clearly focused question.:** Well covered |
| | **1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately |
| | **1.3 An adequate concealment method is used.:** Not addressed |
| | **1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered |
| | **1.5 The treatment and control groups are similar at the start of the trial.:** Well covered |
| | **1.6 The only difference between groups is the treatment under investigation.:** Not addressed |
| | **1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered |
| | **1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** >50% 51% |
| | **1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Well covered |
| | **1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not addressed |
| | **2.1 How well was the study done to minimise bias?: +** |

| | |
|---|---|
| **Study ID** | **ZIMBROFF2007** |
| **General info** | **Funding source:** Pharmaceutical industry |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |

**Type of analysis:** LOCF

**Type of analysis:** ITT - All randomised participants who were administered at least one dose of double-blind medication.

Also had a per protocol sample which included patients with >=80% adherence to the medication regimen for 2 weeks

**Blindness:** Double-blind dummy tablets were used to ensure blinding

**Duration:** No. weeks of treatment 4

**Raters:** Not stated to be independent of treatment

**Design:** Multi-centre - 25 Centres, US

**Number of people screened, excluded & reasons:** 371 screened, 256 randomised

**Notes about study methods:** Computer-generated centre blocked blinded randomisation list generated by the sponsors and provided to the investigators

**Participants**

**Diagnosis:** Other schizophrenia related [%] Schizoaffective disorder - 23%

**Diagnosis:** Schizophrenia [% of sample] 77%

**Diagnostic tool:** DSM-IV

**Inclusion criteria:**
- Aged 18-70
- Hospitalised <14 consecutive days prior to screening
- >=4 GCI-S, PANSS total >=80 with at least 4 on 2+ PANSS positive item scales.

**Exclusion criteria:**
- <14 days total exposure to ziprasidone or aripiprazole
- Refractory to treatment (defined as a failure to respond to two adequate trials of treatment)
- Serious medical condition
- DSM-IV defined alcohol/substance misuse or dependence in 90-days prior to screening

**Total sample size:** Safety population 253

**Total sample size:** ITT population 247

**Total sample size:** No. randomised 256

**Gender:** % female 33%

**Age:** Mean 40

**Ethnicity:**
[Ziprasidone / Aripiprazole]
Race: N(%)

White: 42(34) / 50(39)
Black: 70(56) / 59(46)
Asian: 3(2) / 1(1)
Other: 10(8) / 18(14)

**Setting:** Inpatient

**History:** Not reported

**Baseline stats:**
[Ziprasidone / Aripiprazole]
BPRS: 57.4(6.3) / 57.4(6.3)

**Interventions**

**Intervention - group 1.:** Ziprasidone, 40-80mg/day, N = 125

**Intervention - group 2.:** Aripiprazole, 10-30mg/day, N = 128

**Notes about the interventions:**
Ziprasidone
Patients received fixed doses for first 2 weeks: 40mg/ twice a day on day 1, 60mg/twice a day on day 2 and 80mg/twice a day on days 3-14. Thereafter dosing of 40, 60 or 80mg/twice a day was permitted

Aripiprazole
Patients received fixed doses for first 2 weeks: 15mg on days 1-14; thereafter dosing of 415 or 30mg/day

**Outcomes**

**Leaving the study early:** Leaving because of adverse effects

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Global state & service outcomes (e.g. CGI):** Average score/change in global state - CGI-S

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS, BPRS

**Adverse events:** Average score/change in specific adverse effects- SAS; BAS

**Adverse events:** Number of people with specific adverse effects with all adverse events reported by >=5%

**Other:** Discharge from hospital
Weight change, metabolic parameters, ECT parameters

**Quality**

**1.1 The study addresses an appropriate and clearly focused question.:** Well covered

**1.2 The assignment of subjects to treatment groups is randomised.:** Well covered

**1.3 An adequate concealment method is used.:** Adequately addressed

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Adequately addressed

**1.5 The treatment and control groups are similar at the start of the trial.:** Adequately addressed

**1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Adequately addressed

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** 20-50%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Well covered

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not addressed

**2.1 How well was the study done to minimise bias?: +**

**References of included studies (update)**

**ATMACA2002**

Atmaca,M.; Kuloglu,M.; Tezcan,E.; Canatan,H.; Gecici,O. (2002) Quetiapine is not associated with increase in prolactin secretion in contrast to haloperidol. *Archives of Medical Research.* 33(**6**): 562 - 565.

**AZORIN2006**

Azorin,J.M.; Strub,N.; Loft,H. (2006) A double-blind, controlled study of sertindole versus risperidone in the treatment of moderate-to-severe schizophrenia. *International Clinical Psychopharmacology.* 21(**1**): 49 - 56.

**BREIER2005**

*Breier,A.; Berg,P.H.; Thakore,J.H.; Naber,D.; Gattaz,W.F.; Cavazzoni,P.; Walker,D.J.; Roychowdhury,S.M.; Kane,J.M. (2005) Olanzapine versus ziprasidone: results of a 28-week double-blind study in patients with schizophrenia. *American Journal of Psychiatry.* 162(**10**): 1879 - 1887.

Phillips,G.A.; Van Brunt,D.L.; Roychowdhury,S.M.; Xu,W.; Naber,D. (2006) The relationship between quality of life and clinical efficacy from a randomized trial comparing olanzapine and ziprasidone. *Journal of Clinical Psychiatry.* 67(**9**): 1397 - 1403.

**CHAN2007B**

Chan,H.Y.; Lin,W.W.; Lin,S.K.; Hwang,T.J.; Su,T.P.; Chiang,S.C.; Hwu,H.G. (2007) Efficacy and safety of aripiprazole in the acute treatment of schizophrenia in Chinese patients with risperidone as an active control: a randomized trial. *The Journal of Clinical Psychiatry* 68: 29 - 36.

**DAVIDSON2007**

Davidson M, Emsley R, Kramer M, Ford L, Pan G, Lim P, Eerdekens M. (2007) Efficacy, safety and early response of paliperidone extended-release tablets (paliperidone ER): results of a 6-week, randomized, placebo-controlled study. *Schizophrenia Research.* 93(**1-3**): 117-130.

**HWANG2003**

Hwang,T.J.; Lee,S.M.; Sun,H.J.; Lin,H.N.; Tsai,S.J.; Lee,Y.C.; Chen,Y.S. (2003) Amisulpride versus risperidone in the treatment of schizophrenic patients: a double-blind pilot study in Taiwan. *Journal of the Formosan Medical Association.* 102(**1**): 30 - 36.

**KANE2002**

Kane,J.M.; Carson,W.H.; Saha,A.R.; McQuade,R.D.; Ingenito,G.G.; Zimbroff,D.L.; Ali,M.W. (2002) Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder.[see comment]. *Journal of Clinical Psychiatry.* 63(**9**): 763 - 771.

**KASPER2003**

*Kasper,S.; Lerman,M.N.; McQuade,R.D.; Saha,A.; Carson,W.H.; Ali,M.; Archibald,D.; Ingenito,G.; Marcus,R.; Pigott,T. (2003) Efficacy and safety of aripiprazole vs. haloperidol for long-term maintenance treatment following acute relapse of schizophrenia. *The International Journal of Neuropsychopharmacology* 6: 325 - 337.

Kane JM, Crandall DT, Marcus RN, Eudicone J, Pikalov A, Carson WH, Swyzen W. (2007) Symptomatic remission in schizophrenia patients treated with aripiprazole or haloperidol for up to 52 weeks. *Schizophrenia Research.* 95: 143-50.

**KANE2007A**

Kane,J.; Canas,F.; Kramer,M.; Ford,L.; Gassmann-Mayer,C.; Lim,P.; Eerdekens,M. (2007) Treatment of schizophrenia with paliperidone extended-release tablets: a 6-week placebo-controlled trial. *Schizophrenia Research.* 90(**1-3**): 147-161.

**KONGSAKON2006**

Kongsakon,R.; Trinidad-Oate,P.; Chaudhry,H.R.; Raza,S.B.; Leynes,C.R.; Khan,I.-U.; Ismail,H.C.; Chan,B.; Ignacio,J.C.; Rodriguez,S.C.; Lowry,A.J.; Brnabic,A.J.M.; Buenaventura,R. (2006) Asian outpatients with schizophrenia: A double-blind randomized comparison of quality of life and clinical outcomes for patients treated with olanzapine or haloperidol. *Journal of the Medical Association of Thailand.* 89(**8**), 1157-1170.

**MARDER2007**

Marder SR, Kramer M, Ford L, Eerdekens E, Lim P, Eerdekens M, Lowy A. (2007) Efficacy and safety of paliperidone extended-release tablets: results of a 6-week, randomized, placebo-controlled study. *Biological Psychiatry.* E-pub ahead of print.

**MARTIN2002**

*Martin,S.; Lo,H.; Peuskens,J.; Thirumalai,S.; Giudicelli,A.; Fleurot,O.; Rein,W.; SOLIANOL Study Group (2002) A double-blind, randomised comparative trial of amisulpride versus olanzapine in the treatment of schizophrenia: short-term results at two months. *Current Medical Research & Opinion.* 18(**6**): 355 - 362.

Mortimer,A.; Martin,S.; Lo,H.; Peuskens,J.; SOLIANOL Study Group (2004) A double-blind, randomized comparative trial of amisulpride versus olanzapine for 6 months in the treatment of schizophrenia. *International Clinical Psychopharmacology.* 19: 63 - 69.

Peuskens,J.; De,HertM; Mortimer,A.; SOLIANOL Study Group (2007) Metabolic control in patients with schizophrenia treated with amisulpride or olanzapine. *International Clinical Psychopharmacology.* 22(**3**): 145 - 152.

**POTKIN2003A**

Potkin,S.G.; Saha,A.R.; Kujawa,M.J.; Carson,W.H.; Ali,M.; Stock,E.; Stringfellow,J.; Ingenito,G.; Marder,S.R. (2003) Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs placebo in patients with schizophrenia and schizoaffective disorder.[see comment]. *Archives of General Psychiatry.* 60(**7**): 681 - 690.

**RIEDEL2007B**

Riedel, M., Müller, N., Spellmann, I., et al. (2007) Efficacy of olanzapine versus quetiapine on cognitive dysfunctions in patients with an acute episode of schizophrenia.. *European Archives of Psychiatry and Clinical Neuroscience.* 257(**7**): 402-12.

**ROSENHECK2003**

Rosenheck,R.; Perlick,D.; Bingham,S.; Liu-Mares,W.; Collins,J.; Warren,S.; Leslie,D.; Allan,E.; Campbell,E.C.; Caroff,S.; Corwin,J.; Davis,L.; Douyon,R.; Dunn,L.; Evans,D.; Frecska,E.; Grabowski,J.; Graeber,D.; Herz,L.; Kwon,K.; Lawson,W.; Mena,F.; et al. (2003) Effectiveness and cost of olanzapine and haloperidol in the treatment of schizophrenia: a randomized controlled trial. *Journal of the American Medical Association.* 290(**20**): 2693 - 2702.

**STUDY-SO36**

Eli Lilly (Study summary on Eli Lilly clinical trials registry) Managing acute schizophrenia, a double-blind comparison between two atypical antipsychotics - Olanzapine and Risperidone.

**WAGNER2005**

Wagner,M.; Quednow,B.B.; Westheide,J.; Schlaepfer,T.E.; Maier,W.; Kuhn,K.U. (2005) Cognitive improvement in schizophrenic patients does not require a serotonergic mechanism: randomized controlled trial of olanzapine vs amisulpride. *Neuropsychopharmacology.* 30(**2**): 381 - 390.

**ZHANG2001**

Zhang, X.Y., Zhou, D.F., Cao, L.Y., et al. (2001) Risperidone versus haloperidol in the treatment of acute exacerbations of chronic inpatients with schizophrenia: A randomized double-blind study. *International Clinical Psychopharmacology* 16: 325-330.

**ZHONG2006**

*Zhong,K.X.; Sweitzer,D.E.; Hamer,R.M.; Lieberman,J.A. (2006) Comparison of quetiapine and risperidone in the treatment of schizophrenia: A randomized, double-blind, flexible-dose, 8-week study. *The Journal of Clinical Psychiatry.* 67: 1093 - 1103.

Harvey,P.D.; Patterson,T.L.; Potter,L.S.; Zhong,K.; Brecher,M. (2006) Improvement in social competence with short-term atypical antipsychotic treatment: a randomized, double-blind comparison of quetiapine versus risperidone for social competence, social cognition, and neuropsychological functioning. *American Journal of Psychiatry.* 163(**11**): 1918 - 1925.

**ZIMBROFF2007**

Zimbroff,D.; Warrington,L.; Loebel,A.; Yang,R.; Siu,C. (2007) Comparison of ziprasidone and aripiprazole in acutely ill patients with schizophrenia or schizoaffective disorder: a randomized, double-blind, 4-week study. *International Clinical Psychopharmacology.* 22(**6**): 363 - 370.

**Characteristics of excluded studies (previous guideline)**

| Study | Reason for exclusion |
|---|---|
| **Anand 1998** | Allocation: randomised<br>Participants: people with treatment-resistant schizophrenia |
| **Arato 1997** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: ziprasidone vs. placebo |
| **Beasley 1996b** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: olanzapine vs. placebo |
| **Beasley 1999** | Allocation: randomised<br>Participants: people with treatment-resistant schizophrenia |
| **Bitter 1999** | Allocation: randomised<br>Participants: people with treatment-resistant schizophrenia |
| **Bondolfi 1998** | Allocation: randomised<br>Participants: people with treatment-resistant schizophrenia |
| **Borison 1996 (USA 006)** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: quetiapine vs. placebo |
| **Boyer 1995** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: amisulpride vs. placebo |
| **Breier 1999** | Allocation: randomised<br>Participants: people with treatment-resistant schizophrenia |
| **Brook 1998** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: ziprasidone vs. haloperidol |
| **Buchanan 1998** | Allocation: randomised<br>Participants: people with treatment-resistant schizophrenia |
| **Chiu 1976** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant)<br>Interventions: clozapine vs. chlorpromazine |

| | |
|---|---|
| **Chow 2000** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant)<br>Interventions: clozapine vs. usual medication |
| **Chowdury 1999** | Allocation: randomised<br>Participants: people with treatment-resistant schizophrenia |
| **Ciurezu 1976** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant)<br>Interventions: clozapine vs. haloperidol |
| **Claghorn 1987** | Allocation: randomised<br>Participants: people with treatment-resistant schizophrenia |
| **Cooper 1999b** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: zotepine vs. placebo |
| **Cosar 1999** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant)<br>Interventions: clozapine vs. sulpiride |
| **Covington 2000** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant)<br>Interventions: clozapine vs. haloperidol |
| **Daniel 1999** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: ziprasidone vs. placebo |
| **Danion 1998** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: amisulpride vs. placebo |
| **Dieterle 1999** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: zotepine vs. perazine |
| **Erlandsen 1981** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant)<br>Interventions: clozapine vs. haloperidol |
| **Essock 1996a** | Allocation: randomised<br>Participants: people with treatment-resistant schizophrenia |

| | |
|---|---|
| **Fabre 1995 (USA 004)** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: quetiapine vs. placebo |
| **Fischer 1999** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: zotepine vs. placebo |
| **Fisher-Cornelssen 1974** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant)<br>Interventions: clozapine vs. chlorpromazine |
| **Fisher-Cornelssen 1976a** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant)<br>Interventions: clozapine vs. clopenthixol |
| **Fisher-Cornelssen 1976b** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant)<br>Interventions: clozapine vs. trifluoperazine |
| **Fleischhacker 1995 (Multi-country)** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: quetiapine vs. quetiapine |
| **Fleming 1998** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant)<br>Interventions: clozapine vs. olanzapine |
| **Gelenberg 1979b** | Allocation: randomised<br>Participants: people with treatment-resistant schizophrenia |
| **Gerlach 1974** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant)<br>Interventions: clozapine vs. haloperidol |
| **Gerlach 1975** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant)<br>Interventions: clozapine vs. haloperidol |
| **Goff 1998** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: ziprasidone vs. haloperidol |
| **Guirguis 1977** | Allocation: randomised |

| | |
|---|---|
| | Participants: people with schizophrenia (not treatment-resistant)<br>Interventions: clozapine vs. chlorpromazine |
| **Gunnar 1999** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: ziprasidone vs. haloperidol |
| **HGCF 2001** | Allocation: randomised<br>Participants: people with treatment-resistant schizophrenia |
| **Hirsch 1999** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: ziprasidone vs. haloperidol |
| **Hong 1997** | Allocation: randomised<br>Participants: people with treatment-resistant schizophrenia |
| **Honifeld 1984** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant)<br>Interventions: clozapine vs. haloperidol |
| **Howanitz 1999** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant)<br>Interventions: clozapine vs. chlorpromazine |
| **Itoh 1977** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant)<br>Interventions: clozapine vs. haloperidol |
| **Kane 1988** | Allocation: randomised<br>Participants: people with treatment-resistant schizophrenia |
| **Kane 1994b** | Allocation: randomised<br>Participants: people with treatment-resistant schizophrenia |
| **Keck 1998** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: ziprasidone vs. placebo |
| **Klieser 1989** | Allocation: randomised<br>Participants: people with treatment-resistant schizophrenia |
| **Klieser 1994** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant)<br>Interventions: clozapine vs. haloperidol vs. remoxipride |

| | |
|---|---|
| **Kudo 1999** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: quetiapine vs. mosaprimine |
| **Kumra 1996b** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant)<br>Interventions: clozapine vs. haloperidol |
| **Lee 1994c** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant)<br>Interventions: clozapine vs. various conventional antipsychotics |
| **Leon 1974** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant)<br>Interventions: clozapine vs. chlorpromazine |
| **Loo 1997** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: amisulpride vs. placebo |
| **Martinot 1995** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: amisulpride vs. placebo |
| **Meyer-Lindenberg 1996** | Allocation: randomised<br>Participants: people with treatment-resistant schizophrenia |
| **Oliemeulen 2000** | Allocation: randomised<br>Participants: people with treatment-resistant schizophrenia |
| **Rosenheck 1997** | Allocation: randomised<br>Participants: people with treatment-resistant schizophrenia |
| **Salganik 1998** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant)<br>Interventions: clozapine vs. haloperidol |
| **Sarai 1987** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: zotepine vs. thioxithene |
| **Shopsin 1979a** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant)<br>Interventions: clozapine vs. chlorpromazine |

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|---|---|
| **Singer 1974** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant)<br>Interventions: clozapine vs. chlorpromazine |
| **Small 1997 (USA-Europe 008)** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: quetiapine vs. placebo |
| **Study 128-104 (unpublished)** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: ziprasidone vs. placebo |
| **Study 128-108 (unpublished)** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: ziprasidone vs. haloperidol |
| **Study 128-115 (unpublished)** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: ziprasidone vs. haloperidol |
| **Study 128-117 (unpublished)** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: ziprasidone vs. risperidone |
| **Study 128-301 (unpublished)** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: ziprasidone vs. haloperidol |
| **Study 128-302 (unpublished)** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: ziprasidone vs. risperidone |
| **Study 128-305 (unpublished)** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: ziprasidone vs. amisulpride |
| **Study BPI1201** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: zotepine vs. placebo |
| **Study NY-97-001 (unpublished)** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: ziprasidone vs. placebo |

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|---|---|
| **Study R-0548 (unpublished)** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: olanzapine vs. ziprasidone |
| **Swift 1998** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: ziprasidone vs. haloperidol |
| **Tamminga 1994d** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant)<br>Interventions: clozapine vs. haloperidol |
| **Wahlbeck 2000** | Allocation: randomised<br>Participants: people with treatment-resistant schizophrenia |
| **Wetzel 1991** | Allocation: randomised<br>Participants: people with schizophrenia<br>Interventions: zotepine vs. perazine |
| **Xu 1985** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant)<br>Interventions: clozapine vs. chlorpromazine |
| **Xu 1989** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant)<br>Interventions: clozapine vs. chlorpromazine |
| **Xu 1994** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant)<br>Interventions: clozapine vs. thioridazine |

**References of excluded studies (previous guideline)**

**Anand 1998**

Anand R, Alphs L, Azorin JM, Remington G, Pere JJ, Bourdeix I. (1998) Superior efficacy of clozapine in chronic severe schizophrenia: comparison with risperidone. Highlights. Journal of Clinical Psychiatry; 60(suppl 12):3-50.

**Arato 1997**

Arato M, O'Connor R, Meltzer H, Bradbury J. (1997) Ziprasidone: efficacy in the prevention of relapse and in the long-term treatment of negative symptoms of chronic schizophrenia. In: *10th European College of Neuropsychopharmacology Congress*; 13-17 Sept 1997; Vienna, Austria.

**Beasley 1996b**

Beasley JCM, Sanger T, Satterlee W, Tollefson G, Tran P, Hamilton S. (1996) Olanzapine versus placebo: Results of a double-blind, fixed dose olanzapine trial. *Psychopharmacology*; 124:159-167.

**Beasley 1999**

Beasley CM, Beuzen JN, Birkett MA, Kiesler GM, Tollefson GD, Wood AJ. (1999) Olanzapine versus clozapine: an international double-blind study of the treatment of resistant schizophrenia. In: *152nd Annual Meeting of the American Psychiatric Association*; 15 - 20 May 1999; Washington DC, US.

**Bitter 1999**

Bitter I, Brook S, Dossenbach M, Janka Z, Banki CM, Selemani S, et al. (1999) Olanzapine versus clozapine in patients non-responsive or intolerant to standard acceptable treatment of schizophrenia. *European Neuropsychopharmacology*; 9(suppl. 5): S288-S289.

**Bondolfi 1998**

Bondolfi G, Dufour H, Patris M, May JP, Billeter U, Eap CB, et al. (1998) Risperidone versus clozapine in treatment-resistant chronic schizophrenia: a randomised double-blind study. *American Journal of Psychiatry*; 155(4):499-504.

**Borison 1996 (USA 006)**

Borison RL, Arvanitis LA, Miller BG. (1996) ICI 204,636, an atypical antipsychotic: efficacy and safety in a multicenter, placebo-controlled trial in patients with schizophrenia. U.S. Seroquel Study Group. *Journal of Clinical Psychopharmacology*; 16(2):158-169.

**Boyer 1995**

Boyer P, Lecrubier Y, Puech AJ, Dewailly J, Aubin F. (1995) Treatment of negative symptoms in schizophrenia with amisulpride. *British Journal of Psychiatry;* 166:68-72.

**Breier 1999**

Breier AF, Malhotra AK, Su TP, Pinals DA, Elman I, Adler CM, et al. (1999) Clozapine and risperidone in chronic schizophrenia: effects on symptoms, parkinsonian side effects, and neuroendocrine response. *American Journal of Psychiatry*; 156(2):294-8.

**Brook 1998**

Brook S, Krams M, Gunn KP. (1999) The efficacy and tolerability of intramuscular (im) ziprasidone versus im haloperidol in patients with acute, nonorganic psychosis (abstract). *Schizophrenia Research*; 1(2-3):933-941.

**Buchanan 1998**

Buchanan RW, Breier A, Kirkpatrick B, Ball P, Carpenter WT.(1998) Positive and negative symptom response to clozapine in schizophrenic patients with and without the deficit syndrome. *American Journal of Psychiatry*; 155(6):751-760.

**Chiu 1976**

Chiu E, Burrows G, Stevenson J. (1976) Double-blind comparison of clozapine with chlorpromazine in acute schizophrenic illness. *Australian and New Zealand Journal of Psychiatry;* 10(4):343-347.

**Chow 2000**

Chow E, Desai H, Selhi Z, Bassett AS, Collins E. (2000) A study to evaluate the antiaggressive properties of clozapine. *Schizophrenia Research*; 41(1):183.

**Chowdhury 1999**

Chowdhury AN, Mukherjee A, Ghosh K, Chowdhury S, Das Sen K. (1999) Horizon of a new hope: Recovery of schizophrenia in India. *International Medical Journal*; 6(3):181-185.

**Ciurezu 1976**

Ciurezu T, Ionescu R, Nica Udangiu S, Niturad D, Oproiu L, Tudorache D, et al. (1976) Etude clinique en 'double blind' du HF 1854 (LX 100-129, clozapine ou leponex) compare a l'haloperidol. [Double-blind clinical study of HF 1854 (LX 100-129, clozapine or leponex) as compared with haloperidol]. *Neurologie et Psychiatrie ( Bucur*); 14(1):29-34.

**Claghorn 1987**

Claghorn J, Honigfeld G, Abuzzahab FS, Wang R, Steinbook R, Tuason V, et al. (1987) The risks and benefits of clozapine versus chlorpromazine. *Journal of Clinical Psychopharmacology*; 7:377-84.

**Cooper 1999b**

Cooper SJ, Butler A, Tweed J, Welch C, Raniwalla J. (2000) Zotepine in the prevention of recurrence: A randomised, double-blind, placebo-controlled study for chronic schizophrenia. *Psychopharmacology;*150(3):237-243.

**Cosar 1999**

Cosar B, Candansayar S, Taner E, Isik E. (1999) Comparison of efficacy of clozapine, sulpiride, chlorpromazine and haloperidol in chronic schizophrenic patients therapy. *European Neuropsychopharmacology*; 9(suppl. 5):S287.

**Covington 2000**

Covington L, Cola PA. (2000) Clozapine vs. haloperidol: Antipsychotic effects on sexual function in schizophrenia. *Sexuality and Disability*; 18(1):41-48.

**Daniel 1999**

Daniel DG, Zimbroff DL, Potkin SG, Reeves KR, Harrigan EP, Lakshminarayanan M. (1999) Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. Ziprasidone Study Group. *Neuropsychopharmacology*; 20(5):491-505.

**Danion 1998**

Danion JM, Rein W, Fleurot O, Amedro MJ, Amphoux G, Bougerol T, et al. (1999) Improvement of schizophrenic patients with primary negative symptoms treated with amisulpride. *American Journal of Psychiatry*; 156(4):610-616.

**Dieterle 1999**

Dieterle DM, Muller Spahn F, Ackenheil M. (1991) Wirksamkeit und Vertraglichkeit von Zotepin im Doppelblindvergleich mit Perazin bei schizophrenen Patienten. [Effectiveness and tolerance of zotepine in a double-blind comparison with perazine in schizophrenic patients]. *Fortschritte der Neurologie-Psychiatrie*; 59(suppl 1):18-22.

**Erlandsen 1981**

Erlandsen C. (1981) Trial of a new neuroleptic drug, Leponex (clozapine) in long-standing schizophrenia. *Nordisk Psykiatrisk Tidsskrift*; 35(3):248-253.

**Essock 1996**

Essock SM, Hargreaves WA, Covell NH, Goethe J. (1996) Clozapine's effectiveness for patients in state hospitals: results from a randomized trial. *Psychopharmacology Bulletin*; 32:683-97.

**Fabre 1995 (USA 004)**

Fabre LF, Arvanitis L, Pultz J, Jones VM, Malick JB, Slotnick VB. (1995) ICI 204,636, a novel, atypical antipsychotic - early indication of safety and efficacy in patients with chronic and subchronic schizophrenia. *Clinical Therapeutics*; 17(3):366-378.

**Fischer 1999**

Fischer W, Riedel M, Muller N, Moller HJ, the Zotepine Study Group. (2000) Primary negative symptom schizophrenia - a study with the atypical neuroleptic zotepine. *Schizophrenia Research*; 41(1):208.

**Fisher-Cornelssen 1974**

Fischer-Cornelssen K, Ferner U, Steiner H. (1974) Multifokale Psychopharmakaprufung ("Multihospital trial"). *Arzneimittelforschung*; 24:1706-24.

**Fisher-Cornelssen 1976a/b**

Fischer-Cornelssen KA, Ferner UJ. (1976) An example of European multicenter trials: multispectral analysis of clozapine. *Psychopharmacology Bulletin*; 12:34-9.

**Fleischhacker 1995 (Multi-country)**

King DJ, Link CGG, Kowalcyk B. (1998) A comparison of bd and tid dose regimens of quetiapine ('Seroquel') in the treatment of schizophrenia. *Psychopharmacology*; 37(2):139-146.

**Fleming 1998**

Fleming K, Potkin SG, Alva G, Carreon D. (1999) Dissociation of improvement in neurocognition and negative symptomatology with olanzapine and clozapine. *Schizophrenia Research*; 36(1-3):279.

**Gelenberg 1979**

Gelenberg AJ, Doller JC. (1979) Clozapine versus chlorpromazine for the treatment of schizophrenia: preliminary results from a double-blind study. *Journal of Clinical Psychiatry*; 40:238-240.

**Gerlach 1974**

Gerlach J, Koppelhus P, Helweg E, Monrad A. (1974) Clozapine and haloperidol in a single-blind cross-over trial: therapeutic and biochemical aspects in the treatment of schizophrenia. *Acta Psychiatrica Scandinavica*; 50:410-24.

**Gerlach 1975**

Gerlach J, Thorsen K, Fog R. (1975) Extrapyramidal reactions and amine metabolites in cerebrospinal fluid during haloperidol and clozapine treatment of schizophrenic patients. *Psychopharmacologia*; 40:341-350.

**Goff 1998**

Goff DC, Posever T, Herz L, Simmons J, Kletti N, Lapierre K, et al. (1998) An exploratory haloperidol-controlled dose-finding study of ziprasidone in hospitalized patients with schizophrenia or schizoaffective disorder. *Journal of Clinical Psychopharmacology*; 18(4):296-304.

**Guirguis 1977**

Guirguis E, Voineskos G, Gray J, Schlieman E. (1977) Clozapine (leponex) vs Chlorpromazine (Largactil) in acute schizophrenia (a double-blind controlled study). *Current Therapeutic Research, Clinical and Experimental*; 21(5):707-719.

**Gunnar 1999**

Larson G. (1999) A phase III open-label study evaluating toleration and safety of ziprasidone vs haloperidol in psychotic disorder. In: *Toxline* [database online]. [cited 2001 6 June]. Bethesda, MD: National Institutes of Health, 1999. Available from: URL: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE

**Hale 2000**

Hale A, Azorin JM, Kasper S, Maier W, Syvalahti E, Van der Burght M, et al. (2000) Sertindole is associated with a low level of extrapyramidal symptoms in schizophrenic patients: Results of a phase III trial. *International Journal of Psychiatry in Clinical Practice*; 4(1):47-54.

Hale A, Azorin JM, Kasper S, Maier W, Syvalahti E, Van der Burght M, et al. (2000) Sertindole improves both the positive and negative symptoms of schizophrenia: Results of a phase III trial. *International Journal of Psychiatry in Clinical Practice*; 4(1):55-62.

**HGCF 2001**

Eli Lilly and Company Limited. (2001) The use of the newer (atypical) antipsychotics in the treatment of schizophrenia: Olanzapine. Submission to: the National Institute for Clinical Excellence. Basingstoke: Eli Lilly and Company Limited, 1 June 2001.

**Hirsch 1999**

Hirsch SR, Power A. (1999) A 28-week comparison of ziprasidone and haloperidol in outpatients with stable schizophrenia. In: *152nd Annual Meeting of the American Psychiatric Association*; 15 - 20 May 1999; Washington DC, US.

**Honigfeld 1984**

Honigfeld G, Patin J, Singer J. (1984) Clozapine: antipsychotic activity in treatment resistant schizophrenics. *Advances in Therapy*; 1(2):77-97.

**Howanitz 1999**

Howanitz E, Pardo M, Smelson DA, Engelhart C, Eisenstein N, Losonczy ME. (1999) The efficacy and safety of clozapine versus chlorpromazine in geriatric schizophrenia. *Journal of Clinical Psychiatry*; 60(1):41-44.

**Hong 1997**

Hong CJ, Chen JY, Sim CB. (1997) A double-blind comparative study of clozapine versus chlorpromazine on Chinese patients with treatment-refractory schizophrenia. *International Clinical Psychopharmacology*; 12(3):123-130.

**Itoh 1977**

Itoh H, Miura S, Yagi G, Sakurai S, Ohtsuka N. (1977) Some methodological considerations for the clinical evaluation of neuroleptics--comparative effects of clozapine and haloperidol on schizophrenics. *Folia Psychiatrica et Neurologica Japonica*; 31(1):17-24.

**Kane 1988**

Kane JM, Honigfeld G, Singer J, Meltzer H. (1998) Clozapine in treatment-resistant schizophrenics. *Psychopharmacology Bulletin*; 24(1):62-67.

**Kane 1994b**

Kane JM, Schooler NR, Marder S, Wirshing W, Ames D, Umbricht D, et al. (1996) Efficacy of clozapine versus haloperidol in a long-term clinical trial. *Schizophrenia Research*; 18:127.

**Keck 1998**

Keck P, Buffenstein A, Ferguson J, Feighner J, Jaffe W, Harrigan EP, et al. (1998) Ziprasidone 40 and 120 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 4-week placebo-controlled trial. *Psychopharmacology* (Berl.); 140(2):173-84.

**Klieser 1989**

Klieser E, Schonell H. (1990) Klinisch-pharmakologische Studien zur Behandlung schizophrener Minussymptomatik. In: Moller HJ, Pelzer E, editors. *Neuere Ansatze zur Diagnostik und Therapie schizophrener Minussymptomatik*. Berlin: Springer-Verlag.

**Klieser 1994**

Klieser E, Strauss WH, Lemmer W. The tolerability and efficacy of the atypical neuroleptic remoxipride compared with clozapine and haloperidol in acute schizophrenia. *Acta Psychiatrica Scandinavica*; 89(suppl 380):68-73.

**Kudo 1999**

Kudo Y, Nomura J, Ikawa G, Nakajima T, Saito M, Sakai T, et al. (1999) Clinical trial of quetiapine in schizophrenia - efficacy and tolerability of quetiapine: a comparative double-blind study with masopramine in schizophrenia patients. In: *Annual Meeting of the World Psychiatric Association*; August 6-11 1999; Hamburg, Germany.

**Kumra 1996**

Kumra S, Frazier JA, Jacobsen LK, McKenna K, Gordon CT, Lenane MC, et al. (1996) Childhood-onset schizophrenia. A double-blind clozapine-haloperidol comparison. *Archives of General Psychiatry*; 53(12):1090-7.

**Lee 1994**

Lee M, Thompson P, Meltzer H. (1994) Effects of clozapine on cognitive function in schizophrenia. *Journal of Clinical Psychiatry*; 55(sB):82-87.

**Leon 1974**

Leon CA, Estrada H. (1974) Therapeutic effect of clozapine on psychotic symptoms (clinical evaluation using the double-blind method). *Revista Columbiana de Psiquiatria*; 3:309-320.

**Loo 1997**

Loo H, Poirier-Littre MF, et al. (1994) Amisulpride versus placebo in the long-term treatment of negative schizophrenia. *European Psychiatry*; 9(suppl. 1):154S.

**Martinot 1995**

Paillere Martinot M, Lecrubier Y, Martinot JL, Aubin F. (1995) Improvement of some schizophrenic deficit symptoms with low doses of amisulpride. *American Journal of Psychiatry*; 152:130-4.

**Meyer-Lindenberg 1996**

Meyer-Lindenberg A, Bauer U, Lis S, Krieger S, Gallhofer B. (1997) Improvement of cognitive function in schizophrenic patients receiving clozapine or zotepine: Results from a double-blind study. *Pharmacopsychiatry*; 30(2):35-42.

**Oliemeulen 2000**

Oliemeulen EAP, van Hoof JJM, Jogems-Kosterman BJM, Hulstijn W, Tuynman-Qua HG. (2000) Is olanzapine a substitute for clozapine? The effects on psychomotor performance. *Schizophrenia Research*; 41(1):187.

**Rosenheck 1997**

Rosenheck R, Cramer J, Weichun XU, Thomas J, Henderson W, Frisman L, et al. (1997) A comparison of clozapine and haloperidol in hospitalised patients with refractory schizophrenia. *New England Journal of Medicine*; 337:809-15.

**Salganik 1998**

Salganik I, Modai I, Bercovici BR, Kutzuk D, Weizman A. (1998) Clozapine vs haloperidol therapy in elderly chronic schizophrenic inpatients - Preliminary results. A double-blind, cross-over randomized study. *International Journal of Geriatric Psychopharmacology*; 1(4):185-187.

**Sarai 1987**

Sarai K, Okada M. (1987) Comparison of efficacy of zotepine and thiothixene in schizophrenia in a double-blind study. *Pharmacopsychiatry*; 20(1):38-46.

**Shopsin 1979**

Shopsin B, Klein H, Aaronsom M, Collora M. (1979) Clozapine, chlorpromazine, and placebo in newly hospitalized, acutely schizophrenic patients: a controlled, double-blind comparison. *Archives of General Psychiatry*; 36:657-64.

**Singer 1974**

Singer K, Law S. (1974) Comparative double-blind study with clozapine (Leponex) and chlorpromazine in acute schizophrenia. *Journal of International Medical Research;* 2:433-5.

**Small 1997 (USA-Europe 008)**

Small JG, Hirsch SR, Arvanitis LA, Miller BG, Link CG. (1997) Quetiapine in patients with schizophrenia. A high- and low-dose double-blind comparison with placebo. Seroquel Study Group. *Archives of General Psychiatry*; 54 (6):549-57.

**Study 128-104 (unpublished)**

Pfizer (1997) Phase II four week, double-blind, placebo-controlled study evaluating the efficacy and safety of three doses of oral CP-88,059-1 in the acute exacerbation of schizophrenia and schizoaffective disorder. Report No: 128-104. Sandwich: Pfizer, 5 February, 1997.

**Study 128-108 (unpublished)**

Pfizer (2000) Final study report: ziprasidone protocol 128-108. Forty week, double-blind study evaluating the safety and efficacy of two dose regimens of oral ziprasidone (CP, 88,059-1) (80-120mg, qd and 40-80mg bid) and haloperidol (5-20 mg daily) in the maintenance treatment of outpatients with schizophrenia or schizoaffective disorder. Report No: 128-108. Sandwich: Pfizer, 17 March, 2000.

**Study 128-115 (unpublished)**

Pfizer (1997) Phase III six-week, double-blind, multicenter, placebo-controlled study evaluating the efficacy and safety of three fixed doses of oral ziprasidone (Cp-88059-1) (20 mg, bid, 60mg, bid and 100 mg, bid) and haloperidol in the acute exacerbation of schizophrenia and schizoaffective disorder. Report No: 128-115. Sandwich: Pfizer, 28 February, 1997.

**Study 128-117 (unpublished)**

Pfizer (1998) Fifty-two week, open-label, randomized study evaluating the safety and efficacy of oral ziprasidone (CP-88,059-1) (40-80 mg, bid) and risperidone (3-5 mg, bid) in the maintenance treatment of outpatients with schizophrenia or schizoaffective disorder. Report No: 128-117. Sandwich: Pfizer, 15 December, 1998.

**Study 128-301 (unpublished)**

Pfizer (1997) Twelve week multicentre double-blind fixed dose study comparing ziprasidone with haloperidol in the treatment of patients with acute exacerbation of schizophrenia or schizoaffective disorder. Report No: 128-301. Sandwich: Pfizer, 18 December, 1997.

**Study 128-302 (unpublished)**

Pfizer (1997) Eight week multicentre double-blind study comparing ziprasidone with risperidone in the treatment of patients with acute exacerbation of schizophrenia or schizoaffective disorder. Report No: 128-302. Sandwich: Pfizer, 8 May, 1997.

**Study 128-305 (unpublished)**

Pfizer (1998) Twelve week multi-centre double-blind study comparing the negative symptom efficacy and toleration of ziprasidone and amisulpride in the treatment of patients with chronic schizophrenia. Report No: 128-305. Sandwich: Pfizer, 1 May, 1998.

**Study BPI1201**

Laboratoires Knoll France (2001) Multicentre, double blind, parallel-group comparative study of zotepine versus haloperidol, evaluating costs, quality of life and efficacy in patients with chronic or subchronic schizophrenia. Report No: Study No. ZT 4002. Levallois-Perret: Laboratoires Knoll France, 2001..

**Study NY-97-001 (unpublished) / Study R-0548 (unpublished)**

Pfizer (2001) Appraisal on newer (atypical) antipsychotic drugs in the treatment of schizophrenia: supplementary information. Submission for ziprasidone. Sandwich: Pfizer, 8 June, 2001.

**Swift 1998**

Swift RH, Harrigan EP, van Kammen D, Casey DE. (1998) A comparison of fixed-dose, intramuscular (IM) ziprasidone with flexible-dose, IM haloperidol. In: *11th European College of Neuropsychopharmacology Congress*; 31 Oct - 4 Nov 1998; Paris, France.

**Tamminga 1994**

Tamminga CA, Thaker GK, Moran M, Kakigi T, Gao XM. (1994) Clozapine in tardive dyskinesia: observations from human and animal model studies. *Journal of Clinical Psychiatry*; 55(suppl B):102-6.

**Wahlbeck 2000**

Wahlbeck K, Cheine M, Tuisku K, Ahokas A, Joffe G, Rimon R. (2000) Risperidone versus clozapine in treatment-resistant schizophrenia: a randomised pilot study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*; 24(6):911-922.

**Wetzel 1991**

Wetzel H, von Bardeleben U, Holsboer F, Benkert O. (1991) Zotepin versus Perazin bei Patienten mit paranoider Schizophrenie: eine doppelblind-kontrollierte Wirksamkeitsprufung. [Zotepine versus perazine in patients with paranoid schizophrenia: a double-blind controlled trial of its effectiveness]. *Fortschritte der Neurologie-Psychiatrie*; 59(suppl 1):23-9.

**Xu 1985**

Xu WR, Bao-long Z, Qui C, Mei-Fang G. (1985) A double-blind study of clozapine and chlorpromazine treatment in the schizophrenics. *Chinese Journal of Nervous and Mental Diseases*; 11(4):222-224.

**Xu 1989**

Potter WZ, Ko GN, Zhang L-D, Yan W. (1989) Clozapine in China: A review and preview of US/PRC collaboration. *Psychopharmacology*; 99(suppl):87-91.

**Xu 1994**

Liu B, Chen Y, Yang D. (1994) Effects of thioridazine on schizophrenics and clinical utility of plasma levels. *Chinese Journal of Neurology and Psychiatry*; 27(6):364-367.

**References of excluded studies (included in previous guideline, but excluded from update)**

**Altamura 1999**

Altamura, A.C., Velona, I., Curreli, R., Bravi, D. (1999). Olanzapine in the treatment of paranoid schizophrenia. *European Neuropsychopharmacology*, 9(suppl 5), S297.

**Barak 2000**

Barak, Y., Shamir, E., Weizman, R. (2000). Risperidone compared with typical neuroleptic treatment in elderly schizophrenic patients. *International Journal of Neuropsychopharmacology*, 3(suppl. 1), S122-S123.

**Borison 1991**

Borison R, et al. (1991) Risperidone versus haloperidol versus placebo in the treatment of schizophrenia. Clinical research report No: RIS-USA-9001, N83170. Piscataway, NJ: Janssen.

**Bouchard 1998**

Bouchard RH, Pourcher E, Merette C, Demers MF, Villeneuve J, Roy MA, et al. (1998) One-year follow-up of schizophrenic patients treated with risperidone or classical neuroleptics: a prospective, randomized, multicentered open-study. *European Neuropsychopharmacology*; 8(suppl. 2):S253.

**Boyer 1990**

Boyer P, Lecrubier Y, Puech AJ. (1990) Treatment of positive and negative symptoms: Pharmacologic approaches. In: Andreasen NC, ed. *Schizophrenia: Positive and Negative Symptoms and Syndromes*, pp. 152-174. Basel, Switzerland: S. Karger AG.

**Breier 2000**

Breier A, Hamilton SH. (2000) Comparative efficacy of olanzapine and haloperidol for patients with treatment-resistant schizophrenia. *Schizophrenia Research*; 41(1):188.

**Breier 2001**

Breier A, Wright P, Birkett J, Meehan KM, David SR, Brook S, et al. (2001) Intramuscular olanzapine: dose-related improvement in acutely agitated patients with schizophrenia (abstract). In: *4th International Meeting of the College of Psychiatric and Neurologic Pharmacists*; March 25-28 2001; San Antonio, Texas. Available from: URL: http://www.cpnp.org/CPNP2001/posters/ [cited: 21 June 2001]

**Colonna (2000)**

Colonna L, Saleem P, Dondey-Nouvel L, Rein W. (2000) Long-term safety and efficacy of amisulpride in subchronic or chronic schizophrenia. Amisulpride Study Group. *International Clinical Psychopharmacology*; 15(1):13-22.

Rein W, L'Heritier C. (1999) Treatment-emergent tardive dyskinesia in the long-term treatment of schizophrenia: a comparison of amisulpride and haloperidol. *European Neuropsychopharmacology*; 9(suppl. 5):S282.

**Conley 1998**

Conley RR, Tamminga CA, Bartko JJ, Richardson C, Peszke M, Lingle J, et al. (1998) Olanzapine compared with chlorpromazine in treatment-resistant schizophrenia. *American Journal of Psychiatry*; 155(7):914-920.

**Csernansky 2000**

Csernansky JG, Mahmoud R, Brenner R. (2000) A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. *New England Journal of Medicine* ; 346:16-22.

Csernansky J, Okamoto A. (2000) Risperidone versus haloperidol for prevention of relapse in schizophrenia and schizoaffective disorders: long-term double-blind comparison. *Schizophrenia Research*; 41(1):198.

Csernansky JG, Okamoto A, Brecher M. (1999) Risperidone vs haloperidol: Prevention of relapse in schizophrenia. *European Neuropsychopharmacology*; 9(suppl. 5):S268.

Csernansky JG, Simpson GM. (2000) A long-term double-blind comparison of risperidone and haloperidol in stable outpatients with schizophrenia or schizoaffective disorder. *International Journal of Psychopharmacology*; 3(suppl 1):S155.

Harvey BH, Stein DJ, Emsley RA. (1999) The new-generation antipsychotics - Integrating the neuropathology and pharmacology of schizophrenia. *South African Medical Journal*; 89(6):661-672.

**Daniel 1998**

Daniel DG, Wozniak P, Mack RJ, McCarthy BG. (1993) Long-term efficacy and safety comparison of sertindole and haloperidol in the treatment of schizophrenia. *Psychopharmacology Bulletin*; 34(1):61-69.

**Emsley 1995**

Emsley RA, McCreadie R, Livingston M, De Smedt G, Lemmens P. (1995) Risperidone in the treatment of first-episode patients with schizophreniform disorder; a double-blind multicentre study. In: *8th European College of Neuro-psychopharmacology Congress*; 30 Sept - 4 Oct 1995; Venice, Italy.

**Emsley 1999 (Multi-country 1999)**

Emsley RA, Raniwalla J, Bailey PJ, Jones AM. (2000) A comparison of the effects of quetiapine ('Seroquel') and haloperidol in schizophrenic patients with a history of and a demonstrated, partial response to conventional antipsychotic treatment. *International Clinical Psychopharmacology*; 15:121-131.

**Gomez 2001**

Gomez JC, Crawford AMK. (2001) Superior efficacy of olanzapine over haloperidol: Analysis of patients with schizophrenia from a multicenter international trial. *Journal of Clinical Psychiatry*; 62(suppl 2):6-11.

**Heck 2000**

Heck AH, Haffmans PMJ, De Groot IW, Hoencamp E. (2000) Risperidone versus haloperidol in psychotic patients with disturbing neuroleptic-induced extrapyramidal symptoms: A double-blind, multi-center trial. *Schizophrenia Research*; 46(2-3):97-105.

**HGBL 1997 unpublished**

HGBL (1997) Eli Lilly. Data on file. Data supplied to the Cochrane Schizophrenia Group 1999.

**HGCQ (Turkey) 2000**

HGCQ (Turkey) (unpublished). Eli Lilly and Company Limited.

**HGDV (Morocco)**

HGDV (Morocco) (unpublished). Eli Lilly and Company Limited.

**HGFH (Korea) 1998**

HGFH (Korea) (1998) Eli Lilly. Data on file. Data supplied to the Cochrane Schizophrenia Group 1999.

**Itoh 1977**

Itoh H, Miura S, Yagi G, Sakurai S, Ohtsuka N. (1977) Some methodological considerations for the clinical evaluation of neuroleptics--comparative effects of clozapine and haloperidol on schizophrenics. *Folia Psychiatrica et Neurologica Japonica*; 31(1):17-24.

**Johnstone 1998**

Johnstone BM, Obenchain RL, Croghan TW, Tunis SL, Kniesner TJ. (1998) To evaluate the cost-effectiveness of olanzapine compared to haloperidol for schizophrenia. In: *151st Annual Meeting of the American Psychiatric Association*; 30 May - 4 June 1998; Toronto, Ontario, Canada.

**Jones 1998**

Jones B. (1998) Olanzapine versus risperidone and haloperidol in the treatment of schizophrenia. In: *151st Annual Meeting of the American Psychiatric Association*; 30 May - 4 June 1998; Toronto, Ontario.

**Kee 1998**

Kee KS, Kern RS, Marshall BD, Green MF. (1998) Risperidone versus haloperidol for perception of emotion in treatment-resistant schizophrenia: preliminary findings. *Schizophrenia Research*; 31(2-3):159-65.

**Kern 1998**

Kern RS, Green MF, Marshall BD, Wirshing WC, Wirshing D, McGurk S, et al. (1998) Risperidone vs. haloperidol on reaction time, manual dexterity, and motor learning in treatment-resistant schizophrenia patients. *Biological Psychiatry*; 44(8):726-32.

**Kern 1999**

Kern RS, Green MF, Marshall BD, Wirshing WC, Wirshing D, McGurk SR, et al. (1999) Risperidone versus haloperidol on secondary memory: can newer medications aid learning? *Schizophrenia Bulletin*; 25(2):223-32.

**Klein 1985**

Klein HE, Dieterle D, Elen E, Hippius H, Nedopie N, Ruther E. (1985) A double blind comparison of amisulpride vs. haloperidol in acute schizophrenic patients. In: *Psychiatry: the State of the Art. Volume 3: Pharmacopsychiatry* (Proceedings of the VII World Congress of Psychiatry, 11-16 July 1983, Vienna, Austria): New York: Plenum Press..

**Kolff 2000**

Kolff M, Coenen A, van Dis H, Duigemans P. (2000) Differential effects of antipsychotic drugs on clinical symptoms and cognitive functions in the treatment of schizophrenia. *European Neuropsychopharmacology*; 10(suppl. 2):S59.

**Lecrubier 1999**

Lecrubier Y, Bouhassira M, Olivier V, Lancrenon S, Crawford AM. (1999) Olanzapine versus amisulpride and placebo in the treatment of negative symptoms and deficit states of chronic schizophrenia. *European Neuropsychopharmacology*; 9(suppl 5):S288.

**Litterell 1999**

Litterell KH (1999) Patients switched from depot antipsychotics to oral risperidone or olanzapine: an open-label randomized trial. In*: 152nd Annual Meeting of the American Psychiatric Association*; 15 - 20 May 1999; Washington DC, US.

**Ljubin 2000**

Ljubin T, Milas DZ, Mimica N, Folnegovic Smalc V, Makaric G. (2000) A preliminary study of the comparative effects of olanzapine and fluphenazine on cognition in schizophrenic patients. *Human Psychopharmacology*; 15(7):513-519.

**Mahmoud 1998**

Mahmoud R, Engelhart L, Deverka P. (1998) Risperidone vs. conventional antipsychotics in usual care: a prospective effectiveness trial of outcomes for patients with schizophrenia and schizoaffective disorder. In: *XXIst Collegium Internationale Neuro-psychopharmacologicum*; 12-16 July 1998; Glasgow.

**Muller (1998)**

Muller MJ, Wetzel H, Benkert O. (1998) Latent dimensions of depressive and negative symptoms in acute schizophrenia: treatment effects of high dose amisulpride vs. flupentixol. *European Neuropsychopharmacology*; 8(suppl. 2):S218.

**Murasaki 1999 (Japan 1999b)**

Murasaki M, Koyama T, Yamauchi T, Yagi MG, Ushijima S, Kamijima K. (1999) Clinical evaluation of quetiapine in schizophrenia - efficacy and tolerability of quetiapine compared with haloperidol in patients with schizophrenia. In: *Annual Meeting of the World Psychiatric Association*; August 6-11, 1999; Hamburg, Germany.

**Quest 2000**

AstraZeneca Pharmaceuticals (2000). Seroquel TM (Quetiapine). Data on file supporting the following claim: 'Seroquel' is as effective as risperidone in the treatment of schizophrenia. Report No: DoF AZ_S0072. Alderley Park, Macclesfield: AstraZeneca Pharmaceuticals.

AstraZeneca Pharmaceuticals (2001) Seroquel TM (Quetiapine). Data on file. Report No: DoF AZ_S0075. Alderley Park, Macclesfield: AstraZeneca Pharmaceuticals.

Mullen J, Jibson MD, Sweitzer D, QUEST Study Group (2001). A comparison of the relative safety, efficacy, and tolerability of quetiapine and risperidone in outpatients with schizophrenia and other psychotic disorders: the quetiapine experience with safety and tolerability (QUEST) study. *Clinical Therapeutics*; 23(11):1839-54.

Mullen J, Reinstein M, Bari M, Ginsberg L, Sandler N. (1999) Quetiapine and risperidone in outpatients with psychotic disorders: results of the QUEST trial. *European Neuropsychopharmacology*; 9(suppl. 5):S267.

Mullen JA, Sajatovic M, Sweitzer D. (2000) Efficacy of quetiapine and risperidone against depressive symptoms in outpatients with psychotic disorders. Poster presented at the American Psychiatric Association (APA) Meeting; May 13-18 2000; Chicago, Illinois.

Reinstein MJ, Ginsberg LD, Sandler NH, Mullen JA, Bari MA. (1999) Quetiapine fumarate and risperidone in outpatients with psychotic disorders: results of the quest trial. In: *152nd Annual Meeting of the American Psychiatric Association*; 15-20 May 1999; Washington DC, US.

Tandon R, Mullen J, Sweitzer D. (2001) Quetiapine and risperidone in outpatients with schizophrenia: subanalysis of the QUEST Trial. Poster NR242 presented at the American Psychiatric Association (APA) Annual Meeting; 2001 May 5-10; New Orleans, Louisiana.

**Rabinowitz 2001**

Rabinowitz J, Hornik T, Davidson M. (2001) Rapid onset of therapeutic effect of risperidone versus haloperidol in a double blind randomized trial. *Journal of Clinical Psychiatry*, in press.

**Speller 1997**

Speller JC, Barnes TRE, Curson DA, Pantelis C, Alberts JL. (1997) One-year, low-dose neuroleptic study of in-patients with chronic schizophrenia characterised by persistent negative symptoms: Amisulpride v. haloperidol. *British Journal of Psychiatry*; 171:564-568.

**Tohen 1999**

Tohen MF, Zhang F, Sanger TM, Gannon KS, Tollefson GD. (1999) Olanzapine versus haloperidol in schizoaffective bipolar disorder: a repeated-measures analysis. In: *152nd Annual Meeting of the American Psychiatric Association*; 15-20 May 1999; Washington DC, US.

**Turjanski 1998**

Turjanski S, Rein W, Theron M. (1998) Onset of action in acute schizophrenia, amisulpride versus haloperidol. In: *11th Congress of the European College of Neuropsychopharmacology*; 31 Oct - 4 Nov 1998; Paris, France.

**Tys 1999**

Tys SM, Vlokh IY. (1999) Influence of risperidone very small doses on the negative symptoms in schizophrenia. *Schizophrenia Research*; 36(1-3):300.

**Van Kammen 1996**

van Kammen DP, McEvoy JP, Targum SD, Kardatzke D, Sebree TB. (1996) A randomized, controlled, dose-ranging trial of sertindole in patients with schizophrenia. *Psychopharmacology*; 124:168-175.

**Velligan 1999**

Velligan Di, Newcomer JW. (1999) Changes in cognitive function with quetiapine fumarate versus haloperidol. In: *152nd Annual Meeting of the American Psychiatric Association.* 15-20th May, 1999. Washington DC, US.

Velligan DI, Newcomer J, Pultz J et al. (2002) Does cognitive function improve the quetiapine in comparison to haloperidol? *Schizophrenia Research*; 53 (3): 239-248.

**Wetzel 1998**

Wetzel H, Grunder G, Hillert A, Philipp M, Gattaz WF, Sauer H, et al. (1998) Amisulpride versus flupentixol in schizophrenia with predominantly positive symptomatology - A double-blind controlled study comparing a selective D-2-like antagonist to a mixed D-1-/D-2-like antagonist. *Psychopharmacology*; 137(3):223-232.

**Wirshing 1999**

Wirshing DA, Marshall BD, Jr., Green MF, Mintz J, Marder SR, Wirshing WC. (1999) Risperidone in treatment-refractory schizophrenia. *American Journal of Psychiatry*; 156(9):1374-9.

**Wright 2000**

Wright P, Birkett M, Ferchland I, David S, Alaka K, Pullen P, et al. (2000) A double-blind study of intramuscular olanzapine, haloperidol and placebo in acutely agitated schizophrenic patients. *European Neuropsychopharmacology*; 10(suppl. 3):S304.

**Zhang 1999**

Zhang F, Tohen M, Gannon KS, Breier A. (1999) Olanzapine versus haloperidol: assessment of cognitive function in patients with schizoaffective disorder, bipolar type. *European Neuropsychopharmacology*; 9(suppl. 5):S247.

Zhang F, Tohen M, Sanger T, Gannon KS, Tollefson GD, Breier A. (1999) Olanzapine versus haloperidol in schizoaffective disorder, bipolar type: a repeated measures analysis. *European Neuropsychopharmacology*; 9(suppl. 5):S246-S247.

# Promoting recovery in people with schizophrenia that is in remission – Relapse prevention

**Characteristics of included studies (previous guideline)**

| Study | Methods | Participants | Interventions | Outcomes | Notes |
|---|---|---|---|---|---|
| **Csernansky1999** | Allocation:<br>Blindness:<br>Duration: 2.5 years<br>Analysis of Drop-outs:<br>Setting: | Diagnosis:<br>N=365<br>Age: mean approx. 40<br>Sex:<br>History: Stable out-patients (clinical judgement & same medication & same residence for 30 days)<br>Exclusions: | 1. Risperidone (5mg)<br>2. Haloperidol (5-20mg) | Relapse definition:<br>1. hospitalisation<br>2. increase of level of care and 20% PANSS increase<br>3. self-injury, suicidal or homicidal ideation, violent behaviour<br>4. CGI>6 | |
| **Speller1997** | Allocation:<br>Blindness:<br>Duration: 52 weeks<br>Analysis of Drop-outs:<br>Setting: | Diagnosis:<br>N=60<br>Age: mean approx 63<br>Sex:<br>History: Chronic, long-term hospitalised inpatients with moderate to severe negative symptoms<br>Exclusions: | 1. Amisulpride (100-800mg)<br>2. Haloperidol (3-20mg) | Relapse definition:<br>1. increase of 3 or more BPRS positive symptom items which did not respond to a dose increase | |
| **Tran1997** | Allocation:<br>Blindness:<br>Duration: 28 weeks<br>Analysis of Drop-outs:<br>Setting: | Diagnosis:<br>N=199<br>Age: not mentioned<br>Sex:<br>History: Initial in- or outpatients who achieved a 20% PANSS reduction<br>Exclusions: | 1. Olanzapine (10-20mg)<br>2. Risperidone (4-12mg) | | Relapse definition:<br>1. Worsening of the PANSS by ≥20% and CGI≥3 |

| | | | | | |
|---|---|---|---|---|---|
| **Tran1998a** | Allocation:<br>Blindness:<br>Duration: 52 weeks<br>Analysis of Drop-outs:<br>Setting: | Diagnosis:<br>N=68<br>Age: mean approx 37<br>Sex:<br>History: responders of the 6 weeks acute phase (at least 40% BPRS reduction or BPRS≥18) who were outpatients at the last visit<br>Exclusions: | 1. Olanzapine (~12mg)<br>2. Haloperidol (~14mg) | | Relapse definition:<br>1. hospitalisation for psychopathology |
| **Tran1998b** | Allocation:<br>Blindness:<br>Duration: 52 weeks<br>Analysis of Drop-outs:<br>Setting: | Diagnosis:<br>N=76<br>Age: mean approx 37<br>Sex:<br>History: responders of the 6 weeks acute phase (at least 40% BPRS reduction or BPRS≥18) who were outpatients at the last visit<br>Exclusions: | 1. Olanzapine (~12mg)<br>2. Haloperidol (~14mg) | | Relapse definition:<br>1. hospitalisation for psychopathology |
| **Tran1998c** | Allocation:<br>Blindness:<br>Duration: 22-84 weeks<br>Analysis of Drop-outs:<br>Setting: | Diagnosis:<br>N=690<br>Age: mean approx 37<br>Sex:<br>History: responders of the 6 weeks acute phase (at least 40% BPRS reduction or BPRS≥18) who were outpatients at the last visit<br>Exclusions: | 1. Olanzapine (5-20mg – mean 14mg)<br>2. Haloperidol (5-20mg – mean 13mg) | | Relapse definition:<br>1. hospitalisation for psychopathology |

**References of included studies (previous guideline)**

**Csernansky2000**

Csernansky J, Okamoto A. (2000) Risperidone vs haloperidol for prevention of relapse in schizophrenia and schizoaffective disorder: a long-term double-blind comparison *Schizophrenia Research*;41:198-9.

**Speller1997**

Speller JC, Barnes TRE, Curson DA, Pantelis C, Alberts JL. (1997) One-year, low-dose neuroleptic study of in-patients with chronic schizophrenia characterised by persistent negative symptoms – Amisulpride v. Haloperidol. *British Journal of Psychiatry*; 171:564-8.

**Tran1997**

Tran PV, Hamilton SH, Kuntz AJ et. al. (1997) Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. *Journal of Clinical Psychopharmacology;* 17:407-18.

**Tran1998a/b/c**

Tran PV, Dellva MA, Tollefson GD, Wently AL, Beasley CM. (1998) Oral olanzapine versus oral haloperidol in the maintenance treatment of schizophrenia and related psychoses. *British Journal of Psychiatry*; 172:499-505.

**Characteristics of included studies (update)**

| **Study ID** | **ARATO2002** |
|---|---|
| **General info** | **Funding source:** Pharmaceutical industry |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** ITT - Received at least one dose |
| | **Type of analysis:** LOCF |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment - 52 |
| | **Raters:** Not stated to be independent of treatment |
| | **Design:** Multi-centre - 26 European centres with long-term care facilities for the mentally ill |
| | **Number of people screened, excluded & reasons:** 329 screened; 294 randomized, received at least one dose of double-blind treatment and included in the analyses. 16 patients from one centre were excluded from analysis because the centre was found to have deviated from the protocol by permitting concomitant conventional antipsychotic treatment. |
| | **Notes about study methods:** Randomisation by computer-generated code |

**Participants**

**Diagnosis:** Schizophrenia [% of sample] 100

**Diagnostic tool:** Other DSM

**Inclusion criteria:**
- Age >=18
- Hospitalised for >=2 months
- CGI Severity scale <=5 (markedly ill)

**Exclusion criteria:**
- Recent acute exacerbation of schizophrenia
- Score of >=5 on items P7 (hostility) or G8 (uncooperativeness) of the PANSS
- Displayed a significant risk of suicide
- Treatment resistance (defined as lack of therapeutic response to a conventional antipsychotic during an acute exacerbation on at least two occasions in the previous 2 years)
- Substance misuse or dependence in the previous 3 months
- Previous ziprasidone treatment
- Previous treatment with depot neuroleptics, unless the last injection had been at least one treatment cycle before entry
- Treatment with an investigational drug within the previous 4 weeks, fluoxetine in the previous 5 weeks, monoamine oxidase inhibitors in the previous 2 weeks, or antidepressants or lithium in the previous week
- If woman of childbearing potential, not using reliable contraception.
- Pregnant or breastfeeding

**Total sample size:** ITT population 294

**Total sample size:** No. randomised 294

**Gender:** % female 27%

**Age:** Range 18-82

**Age:** Mean 48.7

**Setting:** Inpatient

**History:**
[Placebo / 40mg / 80mg / 160mg]
Duration of illness (months): 260 (147) / 275 (166) / 248 (150) / 264 (130)
Current hospitalisation (months): 62 (89) / 72 (116) / 69 (95) / 70 (85)
Previous hospitalisations, n (%): 12.1 (9.6) / 9.5 (8.0) / 8.3 (7.6) / 10.3 (7.4)

**Baseline stats:**
[Placebo / 40mg / 80mg / 160mg]
PANSS Total: 88.4 (10.0) / 84.2 (18.4) / 86.2 (18.6) / 84.5 (18.3)

CGI-S: 4.1 (0.8) / 4.0 (0.7) / 4.0 (0.6) / 4.0 (0.7)
GAF: 46.9 (12.8) / 48.0 (11.7) / 46.9 (12.0) / 47.6 (11.8)

**Notes about participants:** Most patients were taking a conventional antipsychotic. 27 patients were taking clozapine, two were taking quetiapine and one was taking olanzapine.

**Interventions**

**Intervention - group 1.:** Placebo, n=61

**Intervention - group 2.:** Ziprasidone, 40mg/day, n=72

**Intervention - group 3.:** Ziprasidone, 80mg/day, n=68

**Intervention - group 4.:** Ziprasidone, 160mg/day, n=67

**Notes about the interventions:** Patients assigned to 160mg received 80mg for first two days, and 160mg thereafter. No change in dose was permitted during the study. Anticholinergics, lorazepam for agitation and temazepam (upper limit 20 mg) for insomnia, were permitted at the investigator's discretion. All other psychotropic medication was prohibited.

**Outcomes**

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Leaving the study early:** Leaving because of adverse effects

**Global state & service outcomes (e.g. CGI):** Relapse - was prospectively operationalised as either a CGI-I score >=6, or a score >=6 on PANSS items P7 (hostility) or G8 (uncooperativeness) persisting for two successive days. Patients with a CGI-I score of 5 (minimally worse) had evaluations repeated daily for 3 days, and then weekly, until their condition improved (remained in the study), or deteriorated to a score Z6 (withdrawn from the study). In addition, any patient who the investigator considered to be in need of additional treatment for exacerbation of symptoms was withdrawn from the study and offered appropriate treatment. Patients withdrawing under these conditions were prospectively defined as experiencing relapse.

**Global state & service outcomes (e.g. CGI):** Average score/change in global state - CGI-S, GAF

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS

**Adverse events:** Average score/change in specific adverse effects - BAS, SAS, AIMS

**Adverse events:** Number of people with general adverse effects

**Adverse events:** Number of people with specific adverse effects- Large list

**Quality**

**1.1 The study addresses an appropriate and clearly focused question.:** Well covered

**1.2 The assignment of subjects to treatment groups is randomised.:** Well covered

**1.3 An adequate concealment method is used.:** Not addressed

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Adequately addressed

**1.5 The treatment and control groups are similar at the start of the trial.:** Well covered

**1.6 The only difference between groups is the treatment under investigation.:** Well covered

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** >50%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Well covered

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not applicable

**2.1 How well was the study done to minimise bias?:** ++

| **Study ID** | **BEASLEY2003** |
|---|---|
| **General info** | **Secondary report?:** Published version of: Beasley C, Hamilton S, Dossenbach M (2000) Relapse prevention with olanzapine. *European Neuropsychopharmacology*; 10(suppl 3): S304 |
| | **Funding source:** Pharmaceutical industry |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** LOCF |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment 52 |
| | **Raters:** Not stated to be independent of treatment |
| | **Design:** Multi-centre - Croatia, Poland, Romania, Russian Federation, US, Yugoslavia. |
| | **Number of people screened, excluded & reasons:** 583 screened |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 79% (OLZ), 87.3% (PLB) |
| | **Diagnosis:** Other schizophrenia related [%] Schizoaffective: 21% (OLZ), 12.7% (PLB) |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:**<br>- BPRS < 37, outpatient, current maintenance on antipsychotic other than clozapine, lack of specific positive symptoms. |
| | **Total sample size:** No. randomised 326 |
| | **Gender:** % female 46.9% (OLZ), 47.1% (PLB) |
| | **Age:** Mean 36.2 (OLZ), 35.1 (PLB) |
| | **Ethnicity:** 100% white |

| | |
|---|---|
| | **Setting:** Outpatient |
| | **Baseline stats:** 42.2 (OLZ), 43.1 (PLB) |
| **Interventions** | **Intervention - group 1.:** Olanzapine, 10-20 mg/d, n=224 |
| | **Intervention - group 2.:** Placebo, n=102 |
| **Outcomes** | **Global state & service outcomes (e.g. CGI):** Relapse - "A protocol-defined relapse was: (1) increase in any BPRS positive item to >4, and either an absolute increase of >=2 on that specific item from randomisation at visit 16 or an absolute increase of >= 4 on the BPRS positive subscale (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) from randomization at visit 16; or (2) hospitalisation due to positive psychotic symptoms. An a priori secondary definition of relapse was a completed suicide or a serious suicide attempt (as determined by the investigator)." |
| | **Global state & service outcomes (e.g. CGI):** Time to relapse |
| | **Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS |
| | **Quality of Life:** Average score/change in quality of life - Heinrichs-Carpenter Quality of Life Questionnaire |
| **Quality** | **1.1 The study addresses an appropriate and clearly focused question.:** Well covered |
| | **1.2 The assignment of subjects to treatment groups is randomised.:** Adequately addressed |
| | **1.3 An adequate concealment method is used.:** Not addressed |
| | **1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Adequately addressed |
| | **1.5 The treatment and control groups are similar at the start of the trial.:** Adequately addressed |
| | **1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed |
| | **1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered |
| | **1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** <20% |
| | **1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Not addressed |
| | **1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not addressed |
| | **2.1 How well was the study done to minimise bias?:** + |

| | |
|---|---|
| **Study ID** | **COOPER2000** |
| **General info** | **Funding source:** Pharmaceutical industry |
| | **Published or unpublished data?:** Published |

| | |
|---|---|
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** ITT |
| | **Type of analysis:** LOCF |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment 26 |
| | **Raters:** Not stated to be independent of treatment |
| | **Design:** Multi-centre - Six European countries |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 100 |
| | **Diagnostic tool:** Other DSM |
| | **Inclusion criteria:** Score of 3 or more on the CGI-S, had a history of recurrence within the past 18 months and were currently maintained on antipsychotic medication. |
| | **Exclusion criteria:**<br>- significant cardiovascular or electrocardiogram (ECG) abnormality; recent myocardial infarction; renal or hepatic failure; blood dyscrasia; epilepsy; Parkinson's disease; dementia; head trauma or significant neurological illness; severe hypotension or hypertension; prostatic hypertrophy; urinary retention; narrow-angle glaucoma; chronic respiratory disease; asthma<br>- hypersensitivity to antipsychotics;<br>- other significant psychiatric illness;<br>- clinically significant abnormal laboratory values;<br>- alcohol misuse; suicide risk;<br>- pregnancy; lactation; breast neoplasm; prolactin-dependent tumour; significant menstrual irregularity; and hyperprolactinemia. Women of childbearing potential could be included if they were using a reliable form of contraception. |
| | **Total sample size:** No. randomised 121 |
| | **Total sample size:** ITT population 119 |
| | **Total sample size:** Safety population 119 |
| | **Gender:** % female 34% (ZOT), 28% (PLB) |
| | **Age:** Mean 43 (ZOT), 41.6 (PLB) |
| | **Age:** Range 20.6-65.4 (ZOT), 20.5-64.6 (PLB) |
| | **Ethnicity:** 98% white (ZOT), 97% white (PLB) |
| | **Setting:** Inpatient |
| | **Setting:** Outpatient |
| | **Baseline stats:** BPRS = 49.8 (ZOT), 48.4 (PLB) |

| | |
|---|---|
| **Interventions** | **Intervention - group 1.:** Zotepine, 300 mg/d, n=63 |
| | **Intervention - group 2.:** Placebo, n=58 |
| **Outcomes** | **Global state & service outcomes (e.g. CGI):** Average score/change in global state - CGI |
| | **Global state & service outcomes (e.g. CGI):** Relapse - 'recurrence' was defined according to the following operationalised criteria: (i) a moderate clinical deterioration from baseline (an increase in CGI severity score of at least 2 points plus an increase of 2 points in at least two positive symptom items on the BPRS) persisting for two assessments over 3 days, but not requiring hospitalisation; (ii) deterioration requiring hospitalisation accompanied, on one assessment, by an increase in CGI severity score of at least 2 points plus an increase of 2 points in at least two positive symptom items on the BPRS; and (iii) severe clinical deterioration (an increase in CGI severity score to 'severely ill' for 24 hours, or, if in hospital, requiring special observation for suicidal or aggressive behaviour). |
| | **Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - BPRS, SANS |
| | **Adverse events:** Average score/change in specific adverse effects |
| | **Adverse events:** Number of people with specific adverse effects |
| **Quality** | **1.1 The study addresses an appropriate and clearly focused question.:** Well covered |
| | **1.2 The assignment of subjects to treatment groups is randomised.:** Well covered |
| | **1.3 An adequate concealment method is used.:** Not addressed |
| | **1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered |
| | **1.5 The treatment and control groups are similar at the start of the trial.:** Adequately addressed |
| | **1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed |
| | **1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered |
| | **1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** >50% |
| | **1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Adequately addressed |
| | **1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not addressed |
| | **2.1 How well was the study done to minimise bias?: +** |

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|---|---|
| **Study ID** | **DELLVA1997** |
| | **Type of study:** Study 1: 46-week double-blind extension (N=58) of acute phase trial (Beasley1996a); Study 2: 46-week double-blind extension (N=62) of acute phase trial (Beasley1997) |

| Study ID | KRAMER2007 |
|---|---|
| General info | **Funding source:** Pharmaceutical industry |
| | **Published or unpublished data?:** Published |
| Method | **Type of study:** Individual randomised trial |
| | **Type of analysis:** ITT |
| | **Type of analysis:** LOCF |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment. Patients remained in the double-blind phase until they experienced a recurrence event, until they withdrew from the study, or until the study was completed (study was terminated prematurely based on significant efficacy results as determined by the independent data monitoring committee). |
| | **Design:** Multi-centre 45 Centres in 6 countries: US, Romania, Turkey, Latvia, Lithuania, and India |
| | **Number of people screened, excluded & reasons:** 628 screened (98 screen failures), 530 included in run-in phase, 312 included in stabilisation phase. |
| | **Notes about study methods:**<br>"5 phases: screening; an 8-week run-in phase, during which eligible patients were hospitalized and received open-label paliperidone ER (3–15 mg once daily, starting dose = 9 mg) until they were deemed stable (minimum of 2 weeks); a 6-week open-label stabilization phase, during which discharged patients remained on their previous dose; a double-blind treatment phase of variable duration, during which stabilized patients were randomized 1:1 (via a sponsor-prepared, computer generated randomization and stratification scheme, assigned by an interactive voice-response system) to receive paliperidone ER (starting at the dose maintained during stabilization) or placebo; and an optional 52-week, open-label extension." |
| Participants | **Diagnosis:** Schizophrenia [% of sample] 100% |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:** Diagnosis of schizophrenia for at least 1 year and were experiencing an acute episode of schizophrenia (Positive and Negative Syndrome Scale [PANSS] total score, 70–120). |
| | **Exclusion criteria:**<br>- DSM-IV Axis I diagnosis other than schizophrenia,<br>- DSM-IV Axis I diagnosis of substance dependence (except nicotine or caffeine) within 6 months before screening,<br>- Significant risk of suicidal or aggressive behavior.<br>- medical conditions that could potentially alter the absorption, metabolism, or excretion of the study medication; relevant history of |

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| | significant or unstable disease; known allergic reactions to barbiturates, carbamazepine, lamotrigine, phenytoin, paliperidone, or risperidone;<br>- previous lack of response to risperidone;<br>- used a depot antipsychotic within 120 days or exposure to experimental treatment within 90 days before screening;<br>- electroconvulsive treatment within 3 months before screening; or had involuntary admission to a psychiatric hospital.<br>- Women were excluded if pregnant, nursing, or planning to become pregnant. |
| | **Total sample size:** No. randomised 207 |
| | **Total sample size:** Safety population 205 |
| | **Total sample size:** ITT population 205 |
| | **Gender:** % female 41% |
| | **Age:** Mean 39 (PAL), 37.5 (PLB) |
| | **Ethnicity:** 60% white, 8.5% black |
| | **Setting:** Inpatient |
| | **Setting:** Outpatient |
| | **Baseline stats:** Paliperidone, |
| **Interventions** | **Intervention - group 1.:** Paliperidone (3-15 mg/d, starting dose 9 mg/d), n=105 |
| | **Intervention - group 2.:** Placebo, n=102 |
| **Outcomes** | **Global state & service outcomes (e.g. CGI):** Relapse- "Recurrence was based on any one of the following criteria: (1) psychiatric hospitalization (involuntary or voluntary admission); (2) increase in PANSS total score by 25% for 2 consecutive days for patients who scored more than 40 at randomization or a 10-point increase for patients who scored 40 or below at randomization; (3) increase in the Clinical Global Impression-Severity (CGI-S) score to at least 4, for patients who scored 3 or below at randomization, or to at least 5, for patients whose CGI-S scores were 4 at randomization, for 2 consecutive days; (4) deliberate self-injury or aggressive behavior, or suicidal or homicidal ideation and aggressive behavior that was clinically significant; (5) increase in prespecified individual PANSS item scores to at least 5, for patients whose scores were 3 or below at randomization, or to at least 6, for patients whose scores were 4 at randomization, for 2 consecutive days." |
| | **Global state & service outcomes (e.g. CGI):** Average score/change in global state - CGI |
| | **Global state & service outcomes (e.g. CGI):** Time to relapse |
| | **Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS |
| | **General and psychosocial functioning (e.g. SFS):** Average score/change in general functioning - Schizophrenia Quality-of-Life Scale and sleep visual analog scale |
| | **Adverse events:** Number of people with specific adverse effects |

| | |
|---|---|
| **Quality** | **1.1 The study addresses an appropriate and clearly focused question.:** Well covered |
| | **1.2 The assignment of subjects to treatment groups is randomised.:** Well covered |
| | **1.3 An adequate concealment method is used.:** Well covered |
| | **1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered |
| | **1.5 The treatment and control groups are similar at the start of the trial.:** Well covered |
| | **1.6 The only difference between groups is the treatment under investigation.:** Well covered |
| | **1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered |
| | **1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** <20% |
| | **1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Adequately addressed |
| | **1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not addressed |
| | **2.1 How well was the study done to minimise bias?:** ++ |

| | |
|---|---|
| **Study ID** | **LOO1997** |
| **General info** | **Funding source:** Not mentioned |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** ITT |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment 26 |
| | **Design:** Multi-centre |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 100% |
| | **Diagnostic tool:** Other DSM |
| | **Inclusion criteria:**<br>- aged between 18 and 55 years;<br>- diagnosis of schizophrenia according to DSM-III-R disorganised or residual type; subchronic or chronic; two of Andreasen's negative components present to a marked degree and a score >=60 on the SANS and 50 on the Scale for the Assessment of Positive Symptoms (SAPS). |

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| | **Exclusion criteria:**<br>- any other major DSM-III-R diagnosis,<br>- risk of suicide, alcohol or drug misuse,<br>- Parkinson's or any other severe somatic disease,<br>- Prescription during the past 6 months of amisulpride for at least 30 days at a dose < 400 mg/day were excluded. |
| | **Total sample size:** No. randomised 141 |
| | **Gender:** % female 30 |
| | **Age:** Mean 34 |
| | **Ethnicity:** 90% white |
| | **Baseline stats:** SANS 81.9 (AMI), 81.5 (PLB) |
| | **Notes about participants:** The majority of the patients (55%) were of the residual type, and 116 (82%) had chronic illness ( > 2 years duration). |
| **Interventions** | **Intervention - group 1.:** Amisulpride, 100 mg/d, n=69 |
| | **Intervention - group 2.:** Placebo, n=72 |
| **Outcomes** | **Leaving the study early:** Leaving because of adverse effects |
| | **Leaving the study early:** Leaving due to any reason (non-adherence to study protocol) |
| | **Global state & service outcomes (e.g. CGI):** Average score/change in global state - GAF |
| | **Global state & service outcomes (e.g. CGI):** Relapse |
| | **Mental state (e.g. BPRS, PANSS, BDI):** Clinically significant response in mental state |
| | **Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - SANS, SAPS |
| | **Adverse events:** Number of people with specific adverse effects |
| **Quality** | **1.1 The study addresses an appropriate and clearly focused question.:** Well covered |
| | **1.2 The assignment of subjects to treatment groups is randomised.:** Adequately addressed |
| | **1.3 An adequate concealment method is used.:** Adequately addressed |
| | **1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Adequately addressed |
| | **1.5 The treatment and control groups are similar at the start of the trial.:** Adequately addressed |
| | **1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed |
| | **1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Adequately addressed |
| | **1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was** |

**completed?:** >50%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Adequately addressed

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not addressed

**2.1 How well was the study done to minimise bias?:** +

| **Study ID** | **MARDER2003** |
|---|---|
| **General info** | **Funding source:** Non-industry support |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** ITT - All randomised participants |
| | **Blindness:** Double-blind Random treatment assignment, using the envelop method, was conducted according to a computer-generated, pseudo-random code, and patients received the morning after discontinuation of existence antipsychotics therapy. |
| | **Duration:** No. weeks of treatment 104 |
| | **Raters:** Not stated to be independent of treatment |
| | **Design:** Multi-centre - Los Angeles, US |
| | **Number of people screened, excluded & reasons:** 110 eligible, 47 not randomised (inadequate stabilisation, unable to tolerate haloperidol, left centre against medical advice, withdrew consent, lost to follow-up, non-compliant with study procedures, moved to a different area, or abused street drugs) |
| | **Notes about study methods:** Randomisation procedure not described |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 100% |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:**<br>- Age 18-60<br>- At least two documented episodes of acute schizophrenic illness, or >=2 years of continuing psychotic symptoms<br>- Had been outpatients for >=1 month<br>- Considered candidates for antipsychotic maintenance therapy |
| | **Total sample size:** ITT population 63 |
| | **Total sample size:** No. randomised 63 |

**Gender:**
% female
[Risperidone / Haloperidol]
12% / 3%

**Age:**
Mean
[Risperidone / Haloperidol]
43.7 (9.2) / 43.3 (8.4)

**Ethnicity:**
[Risperidone / Haloperidol]
Caucasian: 42% / 47%

**Setting:** Outpatient

**History:**
[Risperidone / Haloperidol]
Age at illness onset: 25.3 (6.1) / 24.7 (4.9)

**Baseline stats:** No between-group differences in baseline BPRS

**Interventions**

**Intervention - group 1.:** Risperidone, 2-16mg, n=33

**Intervention - group 2.:** Haloperidol, 2-16mg, n=30

**Notes about the interventions:**
Prior to randomisation, all patients entered a 2-month stabilisation period on open-label haloperidol, which was adjusted to 8mg during the 2 weeks before randomisation.

After randomisation, participants received study drug (risperidone or haloperidol) at 2mg tid for 1st week, then 6mg hs. The dose was titrated (up to max 16mg) on occurrence of psychotic exacerbation and adverse events. Where possible, antiparkinsonian medications were reduced then discontinued.

In addition to randomisation for medication, all participants were also randomised to skills training modules, or skills training with additional In Vivo Amplified Skills Training. (Only pooled results are reported in current study)

Glynn, Marder, Liberman et al (2002) Supplementing clinic-based skills training with manual-based community support sessions: effects on social adjustment of patients with schizophrenia. *American Journal of Psychiatry*, 159, 829-837.

**Outcomes**

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

| | |
|---|---|
| | **Global state & service outcomes (e.g. CGI):** Average score/change in global state - SCL-90 |
| | **Mental state (e.g. BPRS, PANSS, BDI):** Clinically significant response in mental state Psychotic exacerbation defined as >=4 point worsening on sum of BPRS scores for disturbance and hostile-suspiciousness, or >=3 point increase in either cluster |
| | **Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - BPRS, SANS |
| | **General and psychosocial functioning (e.g. SFS):** Average score/change in general functioning - SAS-II (Social Adjustment Scale II) |
| | **Adverse events:** Number of people with specific adverse effects- Use of adjunctive anticholinergics |
| | **Adverse events:** Average score/change in specific adverse effects- SAS, BAS |
| | **Quality of Life:** Average score/change in quality of life - QoL |
| | **Other:** Medication dose |
| **Quality** | **1.1 The study addresses an appropriate and clearly focused question.:** Well covered |
| | **1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately |
| | **1.3 An adequate concealment method is used.:** Not addressed |
| | **1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered |
| | **1.5 The treatment and control groups are similar at the start of the trial.:** Adequately addressed |
| | **1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed |
| | **1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered |
| | **1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** 20-50% |
| | **1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Adequately addressed |
| | **1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not reported adequately |
| | **2.1 How well was the study done to minimise bias?:** + |

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|---|---|
| **Study ID** | **PIGOTT2003** |
| **General info** | **Funding source:** Pharmaceutical industry |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** ITT - All participants with at least one post-baseline assessment |

**Type of analysis:** LOCF

**Blindness:** Double-blind

**Duration:** No. weeks of treatment 26

**Raters:** Not stated to be independent of treatment

**Design:** Multi-centre - 31 centres in US, Czech Republic, Poland, Russia and Ukraine

**Number of people screened, excluded & reasons:** No mention

**Notes about study methods:** No mention of randomisation procedures

**Participants**

**Diagnosis:** Schizophrenia [% of sample] 100%

**Diagnostic tool:** DSM-IV

**Inclusion criteria:**
- Age >=18
- DSM-IV diagnosis of schizophrenia, made at least 2 years prior to entry, with continued antipsychotic treatment during this period to classify diagnoses as chronic
- Stable condition at entry, i.e. no significant improvement or worsening in symptoms in past 3 months, not including those who are doing well or controlled on medication.
- Receiving antipsychotics at entry and have shown response to treatment
- PANSS total >=60 and score <=4 (moderate) on hostility or uncooperativeness subscale
- CGI-S <=4 (moderately ill)
- If female of child-bearing potential, not pregnant and using a reliable form of contraception.

**Exclusion criteria:**
- Experiencing acute relapse
- Psychiatric disorder other than schizophrenia
- History of delirium, dementia, amnesia or a cognitive disorder
- Known treatment resistance to antipsychotics
- Had received fluoxetine within 4 weeks of randomisation
- Dependent on benzodiazepines or had history of alcohol or substance misuse
- Receiving long-acting antipsychotics and the last dose was administered less than one full dosing cycle plus one week ago
- Significant suicide risk
- History of neuroleptic malignant syndrome, thyroid pathology or hypersensitivity to aripiprazole or other quinolinones
- Enrolment in an aripiprazole clinical study or any clinical trial with an investigational agent in past month
- Received ECT in past 2 months.

**Total sample size:** No. randomised 310

**Total sample size:** ITT population 294

**Total sample size:** Safety population 306

**Gender:** % female 44%

**Age:** Mean 42.0

**Age:** Range 18-77

**Ethnicity:** White 91%
Black 7%
Asian/Pacific Islander 1%
Hispanic/Latino 2%

**Setting:** Outpatient

**Setting:** Inpatient

**Baseline stats:**
[Placebo / Aripiprazole]
PANSS: 83.12 / 81.22
CGI-S: 3.55 / 3.49

**Notes about participants:** 3-week placebo washout period

**Interventions**

**Intervention - group 1.:** Placebo, n=155

**Intervention - group 2.:** Aripiprazole, 15mg, n=155

**Notes about the interventions:**
Use of concomitant medication, including neuroleptics, antidepressants, mood stabilisers, benzodiazepines (except lorazepam), beta-adrenergic blockers, antihistamines, and any investigational agent other than study medication was prohibited. Dose tapering of pre-existing concomitant medication was performed, when appropriate, before treatment. Lorazepam, up to max 4mg/day, was permitted for emergent agitation if deemed necessary, and an additional 1-2mg was allowed at night as a sleep aid. Anticholinergics for EPS were permitted if deemed necessary.

**Outcomes**

**Death:** Suicide

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Leaving the study early:** Leaving because of adverse effects

**Global state & service outcomes (e.g. CGI):** Re-hospitalisation

**Global state & service outcomes (e.g. CGI):** Relapse defined as an impending decompensation based any of the following:
1) CGI-I >=5 (minimally worse)
2) PANSS >=5 (moderately severe) on the subscore items of hostility or uncooperativeness on two successive days
3) PANSS total increase >=20%.

**Global state & service outcomes (e.g. CGI):** Time to relapse

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|---|---|
| | **Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS |
| | **Adverse events:** Number of people with general adverse effects- Various, serious AEs |
| | **Adverse events:** Average score/change in specific adverse effects SAS<br>Body weight, glucose, lipids, prolactin, QTc, other laboratory tests and vital signs |
| | **Adverse events:** Number of people with specific adverse effects List of various |
| **Quality** | **1.1 The study addresses an appropriate and clearly focused question.:** Well covered |
| | **1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately |
| | **1.3 An adequate concealment method is used.:** Not addressed |
| | **1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered |
| | **1.5 The treatment and control groups are similar at the start of the trial.:** Well covered |
| | **1.6 The only difference between groups is the treatment under investigation.:** Well covered |
| | **1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered |
| | **1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** >50% |
| | **1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Well covered |
| | **1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not reported adequately |
| | **2.1 How well was the study done to minimise bias?:** + |

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|---|---|
| **Study ID** | **SIMPSON2005[SIMPSON2004]** |
| **General info** | **Secondary report?:** Yes - Continuation of Simpson et al (2004) Randomised controlled, double-blind, multicentre comparison of the efficacy and tolerability of ziprasidone and olanzapine in acutely ill patients with schizophrenia or schizoaffective disorder. *American Journal of Psychiatry*, 161. (Correct 2005, *American Journal of Psychiatry*, 162)<br><br>Responders from the above study were entered into a 6 month continuation study, followed by an optional extension study lasting up to 2 years. |
| | **Funding source:** Pharmaceutical industry |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |

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|---|---|
| **Participants** | **Inclusion criteria:**<br>- completion of 6-weeks double-blind treatment with ziprasidone or olanzapine (in Simpson 2004 study)<br>- a CGI improvement score of <=2 or a >=20% reduction in PANSS at acute-study endpoint<br>- outpatient status<br>**Total sample size:** No. randomised 126 |
| **Study ID** | **SIMPSON2004[Study R-0548]** |
| **General info** | **Secondary report?:** Yes - Pfizer R-0548 (unpublished report included in TA)<br>**Funding source:** Pharmaceutical industry<br>**Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial<br>**Type of analysis:** ITT Participants who took at least one dose of study medication and had a baseline and post-baseline assessment<br>**Type of analysis:** LOCF<br>**Blindness:** Double-blind<br>**Duration:** No. weeks of treatment 6<br>**Raters:** Not stated to be independent of treatment<br>**Design:** Multi-centre US<br>**Number of people screened, excluded & reasons:** 367 screened, 269 randomised and received at least one dose of study medication<br>**Notes about study methods:** Allocation and randomisation procedures not reported |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 63%<br>**Diagnosis:** Other schizophrenia related [%] Schizoaffective 37%<br>**Diagnostic tool:** DSM-IV<br>**Inclusion criteria:**<br>- Aged 18–55<br>- If female, not of childbearing potential<br>- Have been hospitalised for no more than 2 consecutive weeks immediately before screening<br>- Primary diagnosis of schizophrenia or schizoaffective<br>disorder (any subtype, chronic or subchronic) as defined in DSM-IV (diagnostic codes 295.X or 295.70) and persistent psychotic symptoms for the week before hospital admission<br>- At screening, score ≥4 on the CGI severity scale and a score ≥4 on at least one of the following PANSS positive symptom items: |

delusions, conceptual disorganization, or hallucinatory behaviour
- At baseline, score ≥4 on the CGI severity scale and ≥3 on the CGI improvement scale, compared with the screening score. At baseline, patients were also required to meet the criteria for the PANSS positive symptom items that had been used in the screening.
- Normal laboratory test and ECG results
- Negative urine drug screen results at entry.

**Exclusion criteria:**
- Primary DSM-IV axis I psychiatric disorders other than schizophrenia or schizoaffective disorder or DSM-IV-defined psychoactive substance misuse/dependence in the preceding 3 months
- Patients whose depot neuroleptic medication had been discontinued were eligible only after an average dosing period had elapsed.
- Non-response to two adequate treatment trials with antipsychotic medications in the past year
- Judged by the investigator as being at significant risk of suicide, violent behavior, or homicide
- >14 days' total lifetime exposure to olanzapine, those who had received a daily olanzapine dose >10mg, or had discontinued use of this drug due to lack of efficacy or an adverse event.

**Total sample size:** No. randomised 269

**Total sample size:** ITT population - 269?

**Gender:** % female 35%

**Age:** Range 8?-59

**Age:** Mean 38

**Ethnicity:** White 53%
Black 32%
Asian 2%
Hispanic 10%
Other 3%

**Setting:** Inpatient

**History:**
[Ziprasidone / Olanzapine]
Age at first episode: 22.2 (7.0) / 23.7 (8.1)
Years since first onset: 15.4 (9.7) / 14.0 (9.6)

**Baseline stats:**
[Ziprasidone / Olanzapine]
BPRS: 51.5 (9.52) / 50.7 (9.33)
PANSS Total: 90 (16.6) / 89 (16.9)
CGI-S: 4.9 (0.81) / 4.9 (0.79)

CDSS: 6.0 (4.43) / 5.7 (4.94)

**Interventions**

**Intervention - group 1.:** Ziprasidone, mean dose 129.9 (27.3) mg, n=136

**Intervention - group 2.:** Olanzapine, mean dose 11.3 (2.8) mg, n=133

**Notes about the interventions:**
Fixed dosing regimens were used during week 1 only (ziprasidone: 40 mg b.i.d. on days 1 and 2, 80 mg b.i.d. on days 3–7; olanzapine: 5 mg/day on days 1 and 2, 10 mg/day on days 3–7). Dosage was flexible during weeks 2–6 (ziprasidone: 40, 60, or 80 mg b.i.d.; olanzapine: 5, 10, or 15 mg/day). Investigators were allowed to assign doses according to clinical judgment within the permissible range.

Lorazepam was permitted for control of agitation or insomnia, and benztropine was permitted for control of extrapyramidal symptoms.

**Outcomes**

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Leaving the study early:** Leaving because of adverse effects

**Global state & service outcomes (e.g. CGI):** Average score/change in global state - CGI-S, CGI-I

**Mental state (e.g. BPRS, PANSS, BDI):** Clinically significant response in mental state >=20%, 30% and 40% improvements in BPRS

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - BPRS, PANSS, CDSS

**Adverse events:** Number of people with general adverse effects

**Adverse events:** Number of people with specific adverse effects- Various

**Adverse events:** Average score/change in specific adverse effects- ESRS, BAS, AIMS
Body weight, BMI, vital signs, laboratory tests, serum lipid profile, glucose metabolism, uric acid, QTc interval

**Other:** Use of concomitant medications

**Quality**

**1.1 The study addresses an appropriate and clearly focused question.:** Well covered

**1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately

**1.3 An adequate concealment method is used.:** Not addressed

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered

**1.5 The treatment and control groups are similar at the start of the trial.:** Well covered

**1.6 The only difference between groups is the treatment under investigation.:** Well covered

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Adequately addressed

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** 20-50%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Well covered

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not reported adequately
**2.1 How well was the study done to minimise bias?:** ++

| | |
|---|---|
| **Study ID** | **STUDY-S029** |
| **General info** | **Funding source:** Pharmaceutical industry |
| | **Published or unpublished data?:** Unpublished |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** Completer |
| | **Type of analysis:** ITT |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment 52 |
| | **Design:** Multi-centre |
| | **Number of people screened, excluded & reasons:** 314 entered into study |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 100 |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:**<br>- 18-65 years;<br>- outpatients or patients admitted to a hospital for social or practical reasons; received a stable dose of the same conventional antipsychotic drug >=8 weeks before Visit 1; PANSS score >=49 at Visit 2. |
| | **Total sample size:** No. randomised 275 |
| | **Total sample size:** ITT population 274 |
| | **Gender:** % female 33% (OLZ); 26% (HAL) |
| | **Age:** Mean OLZ = 40.7 (10.3) years; HAL = 41.5 (10) years |
| | **Setting:** Outpatient |
| | **Setting:** Inpatient |
| | **Baseline stats:** PANSS total: OLZ = 79.8 (16.5); HAL = 78.4 (16.7) |
| **Interventions** | **Intervention - group 1.:** Olanzapine, 9.8 mg/d, n = 141 |
| | **Intervention - group 2.:** Haloperidol, 8.7 mg/d, n = 134 |

| | |
|---|---|
| **Outcomes** | **Leaving the study early:** Leaving because of adverse effects |
| | **Leaving the study early:** Leaving due to any reason (non-adherence to study protocol) |
| | **Global state & service outcomes (e.g. CGI):** Relapse |
| | **Global state & service outcomes (e.g. CGI):** Average score/change in global state - CGI |
| | **Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS |
| | **General and psychosocial functioning (e.g. SFS):** Average score/change in general functioning - SCD |
| | **Quality of Life:** Average score/change in quality of life - S-QoL |
| **Quality** | **1.1 The study addresses an appropriate and clearly focused question.:** Well covered |
| | **1.2 The assignment of subjects to treatment groups is randomised.:** Adequately addressed |
| | **1.3 An adequate concealment method is used.:** Not addressed |
| | **1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Adequately addressed |
| | **1.5 The treatment and control groups are similar at the start of the trial.:** Adequately addressed |
| | **1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed |
| | **1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Not reported adequately |
| | **1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** >50% |
| | **1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Adequately addressed |
| | **1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not addressed |
| | **2.1 How well was the study done to minimise bias?: +** |

**References of included studies (update)**

**ARATO2002**

Arato M, O'Connor R, Meltzer HY, ZEUS Study Group (2002) A 1-year, double-blind, placebo-controlled trial of ziprasidone 40, 80 and 160 mg/day in chronic schizophrenia: the Ziprasidone Extended Use in Schizophrenia (ZEUS) study. *International Clinical Psychopharmacology*; 17:207–215.

**BEASLEY2003**

Beasley C, Hamilton S, Dossenbach M (2000) Relapse prevention with olanzapine. *European Neuropsychopharmacology*; 10(suppl 3): S304.

*Beasley CM Jr, Sutton VK, Hamilton SH, Walker DJ, Dossenbach M, Taylor CC, Alaka KJ, Bykowski D, Tollefson GD, Olanzapine Relapse Prevention Study Group. (2003). A double-blind, randomized, placebo-controlled trial of olanzapine in the prevention of psychotic relapse. *Journal of Clinical Psychopharmacology* 23(6): 582-94.

**COOPER2000**

Cooper SJ, Butler A, Tweed J, Welch C, Raniwalla J (2000) Zotepine in the prevention of recurrence: a randomised, double-blind, placebo-controlled study for chronic schizophrenia. *Psychopharmacology*; 150:237–243.

**DELLVA1997**

Dellva MA, Tran P, Tollefson GD, Wentley AL, Beasley CM (1997) Standard olanzapine versus placebo and ineffective dose olanzapine in the maintenance treatment of schizophrenia. *Psychiatric Services*; 48:1571–1577.

**KRAMER2007**

*Kramer,M.; Simpson,G.; Maciulis,V.; Kushner,S.; Vijapurkar,U.; Lim,P.; Eerdekens,M. (2007) Paliperidone extended-release tablets for prevention of symptom recurrence in patients with schizophrenia: a randomized, double-blind, placebo-controlled study. *Journal of Clinical Psychopharmacology* 27: 6 - 14.

Kramer,M. (2007) Erratum: Paliperidone extended-release tablets for the prevention of symptom recurrence in patients with schizophrenia: A randomized, double-blind, placebo-controlled study (Journal of Clinical Psychopharmacology (2007) 27 (6-14)). *Journal of Clinical Psychopharmacology.* 27(**3**): 258.

**LOO1997**

Loo H, Poirier-Littre MF, Theron M, Rein W, Fleurot O (1997) Amisulpride versus placebo in the medium-term treatment of the negative symptoms of schizophrenia. *British Journal of Psychiatry*; 170:18–22.

**MARDER2003**

*Marder,S.R.; Glynn,S.M.; Wirshing,W.C.; Wirshing,D.A.; Ross,D.; Widmark,C.; Mintz,J.; Liberman,R.P.; Blair,K.E. (2003) Maintenance treatment of schizophrenia with risperidone or haloperidol: 2-year outcomes. *The American Journal of Psychiatry.* 160: 1405 - 1412.

Green,M.F.; Marder,S.R.; Glynn,S.M.; McGurk,S.R.; Wirshing,W.C.; Wirshing,D.A.; Liberman,R.P.; Mintz,J. (2002) The neurocognitive effects of low-dose haloperidol: a two-year comparison with risperidone. *Biological Psychiatry.* 51: 972 - 978.

**PIGOTT2003**

Pigott,T.A.; Carson,W.H.; Saha,A.R.; Torbeyns,A.F.; Stock,E.G.; Ingenito,G.G.; Aripiprazole Study Group (2003) Aripiprazole for the prevention of relapse in stabilized patients with chronic schizophrenia: a placebo-controlled 26-week study. *Journal of Clinical Psychiatry.* 64(**9**): 1048 - 1056.

**SIMPSON2005**

*Simpson,G.M.; Weiden,P.; Pigott,T.; Murray,S.; Siu,C.O.; Romano,S.J. (2005) Six-month, blinded, multicenter continuation study of ziprasidone versus olanzapine in schizophrenia. *The American Journal of Psychiatry.* 162: 1535 - 1538.

Simpson,G.M.; Glick,I.D.; Weiden,P.J.; Romano,S.J.; Siu,C.O. (2004) Randomized, controlled, double-blind multicenter comparison of the efficacy and tolerability of ziprasidone and olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder. *American Journal of Psychiatry.* 161(**10**): 1837 - 1847.

Harvey,P.D.; Siu,C.O.; Romano,S. (2004) Randomized, controlled, double-blind, multicenter comparison of the cognitive effects of ziprasidone versus olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder. *Psychopharmacology.* 172(**3**): 324 - 332.

**STUDY-S029**

Eli Lilly (Unpublished) A Double-Blind Long-term Study Comparing the Efficacy and Safety of Olanzapine versus Haloperidol in Patients with Schizophrenia Previously Stabilized with Conventional Antipsychotic Treatment.
http://www.clinicalstudyresults.org/drugdetails/viewfile.php?study_name=Trial+6589+A+Double-Blind+Long-

term+Study+Comparing+the+Efficacy+and+Safety+of+Olanzapine+versus+Haloperidol+in+Patients+with+Schizophrenia+Previously+Stabilized+with+Conventional+Ant: Eli Lilly and Company.

**Characteristics of excluded studies (previous guideline)**

| Study | Reason for exclusion |
|---|---|
| **Colonna 2000** | Interventions: Haloperidol vs. Amisulpride<br>Outcomes: no compliance data reported |
| **Daniel 1998** | Interventions: Haloperidol vs. Sertindole |
| **Essock 1996** | Interventions: Clozapine vs. usual care<br>Blinding: not double-blind |
| **Rosenheck 1999** | Interventions: Clozapine vs. Haloperidol |
| **Tamminga 1994** | Interventions: Clozapine vs. Haloperidol |

**References of excluded studies (previous guideline)**

**Colonna 2000**

Colonna L, Saleem P, Dondey-Nouvel L, Rein W. (2000) Long-term safety and efficacy of amisulpride in subchronic or chronic schizophrenia. Amisulpride Study Group. *International Clinical Psychopharmacology*; 15(1):13-22.

Rein W, L'Heritier C. (1999) Treatment-emergent tardive dyskinesia in the long-term treatment of schizophrenia: a comparison of amisulpride and haloperidol. *European Neuropsychopharmacology*; 9(suppl. 5):S282.

**Daniel 1998**

Daniel DG, Wozniak P, Mack RJ, McCarthy BG. (1998) Long-term efficacy and safety comparison of sertindole and haloperidol in the treatment of schizophrenia. *Psychopharmacology Bulletin*; 34(1):61-69.

**Essock 1996**

Essock SM, Hargreaves WA, Covell NH, Goethe J. (1996) Clozapine's effectiveness for patients in state hospitals: results from a randomised trial. *Psychopharmacology Bulletin*; 32:683-97.

**Rosenheck 1999**

Rosenheck R, Evans D, Herz L et al. (1999) How long to wait for a response to clozapine: a comparison of time course of response to clozapine and conventional antipsychotic medication in refractory schizophrenia. *Schizophrenia Bulletin*; 25:709-19.

Rosenheck R, Chang S, Choe Y et al. (2000) Medication continuation and compliance: a comparison of patients treated with clozapine and haloperidol. *Journal of Clinical Psychiatry*; 61:382-6.

**Tamminga 1994**

Tamminga CA, Thaker GK, Moran M, Kakigi T, Gao X-M. (1994) Clozapine in tardive dyskinesia: observations from human and animal model studies. *Journal of Clinical Psychiatry*; 55(suppl.9):102-6.

# Treatment with depot/long-acting injectable antipsychotic medication

**Characteristics of included studies (update)**

| **Study ID** | **CHUE2005** |
|---|---|
| **General info** | **Funding source:** Pharmaceutical industry<br>**Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial<br>**Type of study:** Individual randomised trial (Noninferiority/equivalence)<br>**Type of analysis:** ITT - efficacy data population: defined as patients who had not violated prespecified criteria. The main criterion was that patients received at least 4 injections of long-acting risperidone or placebo.<br><br>Also included a safety population defined as all randomised patients who received at least one injection.<br>**Blindness:** Double-blind<br>**Duration:** No. weeks of treatment 12 (prior to this was an 8-week, open-label run-in period)<br>**Raters:** Not stated to be independent of treatment<br>**Design:** Multi-centre 95 sites in the UK, mainland Europe, North America and Africa<br>**Number of people screened, excluded & reasons:** 779 patients were entered into the run-in period.<br><br>137 were excluded from the double-blind treatment phase, and a further 2 randomised patients did not receive double-blind treatment.<br>**Notes about study methods:** randomisation was stratified according to site, PANSS, ESRS, use of depot antipsychotics in the previous 6 months and daily dose of oral risperidone at randomisation. |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 100%<br>**Diagnostic tool:** DSM-IV<br>**Inclusion criteria:**<br>- aged 18-65<br>- PANSS total >=50<br>- no clinically relevant abnormal biochemistry, haematology or urinalysis laboratory values<br>- remained symptomatically stable as indicated by a stable oral risperidone dose and stable CGI for the last 4 weeks of the run-in period. |

**Exclusion criteria:**
- Moderate or severe symptoms of tardive dyskinesia, history of neuroleptic malignant syndrome.
- known to be unresponsive to risperidone, or required mood stabilisers.
- if treated with clozapine within last 2 months prior to screening, with a depot antipsychotic within one treatment of screening, or with an antidepressant within 30 days before the run-in

**Total sample size:** No. randomised 642

**Total sample size:** ITT population efficacy population (those who had not violated prespecified criteria) - 541

**Gender:** % female 35%

**Age:** Range 18-66

**Age:** Mean 40

**Setting:** Outpatient

**Setting:** Inpatient

**History:**
[Oral risperidone / Long-acting risperidone]
Schizophrenia type n(%)
Paranoid: 195(60.7) / 200(62.7)
Undifferentiated: 56(17.4) / 57(17.9)
Residual: 48(15.0) / 43(13.5)
Disorganised: 20(6.2) / 16(5.0)
Catatonic: 2(0.6) / 3(0.9)
Age at onset: 28.9(0.5) / 28.4(0.5)
n of previous psychiatric hospitalisations: 4.6(0.4) / 5.5(0.4)

**Baseline stats:**
[Oral risperidone / Long-acting risperidone]
PANSS total: 69.3(0.9) / 68.4(1.0)
PANSS positive: 19.1(0.3) / 18.2(0.3)
PANSS negative: 19.7(0.4) / 19.6(0.4)

**Notes about participants:**
During the 6 months prior to run-in 86% had received antipsychotics, including depot antipsychotics (44%) and risperidone (60%)

- 8-week open-label run-in period during which patients were stabilised on oral risperidone. Only patients symptomatically stable were randomised into the two treatment groups.

**Interventions** **Intervention - group 1.:** Oral Risperidone, 1-6mg/day, n=321

**Intervention - group 2.:** Long-acting Risperidone, 25, 50 or 75mg, n=319

**Notes about the interventions:**
During the first 2 weeks of the 8 run-in period, doses of antipsychotics other than risperidone, all anticholinergic medication and propranolol were reduced until discontinued. Other disallowed medications were mood stabilisers, psychostimulants and antidepressants.

During these first 2 weeks all patients received 2, 4 or 6 mg/day of risperidone. Dose adjustment of oral risperidone was allowed according to the investigator's judgment during the first 4 weeks but all patients were maintained on a stable oral dose from weeks 5 to 8.

Oral risperidone:
-patients continued to receive the same oral dose of risperidone as determined by the run-in, plus placebo injection every 2 weeks.

Long-acting risperidone:
-25, 50 or 75 mg of long-acting injectable risperidone every 2 weeks plus oral placebo daily for 12 weeks. Oral supplementation is required during the first weeks of treatment because of the time required to achieve therapeutic serum levels; thus, patients continued to receive active oral risperidone for the first 3 weeks after which they received oral placebo daily for 9 weeks.

**Outcomes**

**Death:** Natural causes

**Leaving the study early:** Leaving because of adverse effects

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Global state & service outcomes (e.g. CGI):** Clinically significant response in global state - CGI - percentage of patients rated as "not ill" or with "mild illness"

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS

**Adverse events:** Average score/change in specific adverse effects- ESRS

**Adverse events:** Number of people with general adverse effects

**Adverse events:** Number of people with specific adverse effects

**Other:** Clinical laboratory tests including haematology, biochemistry, prolactin assay and urinalysis; QTc.

**Quality**

**1.1 The study addresses an appropriate and clearly focused question.:** Well covered

**1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately

**1.3 An adequate concealment method is used.:** Not addressed

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered

**1.5 The treatment and control groups are similar at the start of the trial.:** Well covered

**1.6 The only difference between groups is the treatment under investigation.:** Not addressed

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** <20%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Well covered

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not addressed

**2.1 How well was the study done to minimise bias?:** +

| **Study ID** | **KANE2003** |
|---|---|
| **General info** | **Funding source:** Pharmaceutical industry |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** LOCF |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment 12 |
| | **Raters:** Not stated to be independent of treatment |
| | **Design:** Multi-centre - 41 Centres in the US |
| | **Number of people screened, excluded & reasons:** A total of 554 patients with schizophrenia were screened, of whom 461 entered the 1-week oral risperidone run-in period, and 400 initiated the double-blind phase. |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 100 |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:**<br>- Baseline Positive and Negative Syndrome Scale total scores of 60–120<br>- Good general health<br>- Standard laboratory test results within reference ranges or not clinically significant. |
| | **Exclusion criteria:**<br>- received a depot antipsychotic within 120 days of the start of the trial<br>- were diagnosed as substance dependent, had tardive dyskinesia or a history of neuroleptic malignant syndrome<br>- had a clinically significant ECG abnormality |

- pregnant (or likely to become pregnant) or lactating
- at risk of violent behavior, or had current suicidal ideation
- patients who had a history of severe drug sensitivity or allergy, including sensitivity to risperidone, or who were unresponsive to risperidone were also excluded.

**Total sample size:** No. randomised 400

**Total sample size:** ITT population 370

**Total sample size:** Safety population 400

**Gender:** % female 24.75%

**Age:** Mean The mean ages of the groups were: PLB = 37.7 years (SD=9.4), 25 mg = 38.9 years (SD=9.8), 50 mg = 36.2 years (SD=9.5), 75 mg = 38.1 years (SD=10.7)

**Ethnicity:** African-American: 41.75%
White: 41.5%

**Setting:** Inpatient

**Setting:** Outpatient

**History:** Most (76%) had a diagnosis of paranoid schizophrenia. The number of previous hospitalizations was similar across the four groups (placebo [n=89]: median=4.0, range=0–28; risperidone, 25 mg [n=96]: median=3.5, range=0–99; risperidone, 50 mg [n=101]: median=4.0, range=0–50; risperidone, 75 mg [n=94]: median=4.0, range=0–63). Equal proportions were hospital outpatients and inpatients.

**Baseline stats:** PANSS total: PLB = 82.0 (14.4), 25 mg = 81.7 (12.5), 50 mg = 82.3 (13.9), 75 mg = 80.1 (14.0)

**Interventions** **Intervention - group 1.:** Long-acting risperidone, 25 mg, n = 99

**Intervention - group 2.:** Long-acting risperidone, 50 mg, n = 103

**Intervention - group 3.:** Long-acting risperidone, 75 mg, n = 100

**Intervention - group 4.:** Placebo injection, n = 98

**Outcomes** **Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Leaving the study early:** Leaving because of adverse effects

**Global state & service outcomes (e.g. CGI):** Time to relapse

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS total

**Mental state (e.g. BPRS, PANSS, BDI):** Clinically significant response in mental state >20% improvement in PANSS total

**Adverse events:** Average score/change in specific adverse effects

**Adverse events:** Number of people with specific adverse effects

**Quality** **1.1 The study addresses an appropriate and clearly focused question.:** Well covered

**1.2 The assignment of subjects to treatment groups is randomised.:** Adequately addressed

**1.3 An adequate concealment method is used.:** Not addressed

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered

**1.5 The treatment and control groups are similar at the start of the trial.:** Well covered

**1.6 The only difference between groups is the treatment under investigation.:** Well covered

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** >50%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Not addressed

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not addressed

**2.1 How well was the study done to minimise bias?: +**

**References of included studies (update)**

**CHUE2005**

Chue,P.; Eerdekens,M.; Augustyns,I.; Lachaux,B.; Molcan,P.; Eriksson,L.; Pretorius,H.; David,A.S. (2005) Comparative efficacy and safety of long-acting risperidone and risperidone oral tablets. *European Neuropsychopharmacology.* 15: 111 - 117.

**KANE2003**

Kane,J.M.; Eerdekens,M.; Lindenmayer,J.P.; Keith,S.J.; Lesem,M.; Karcher,K. (2003) Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. *The American Journal of Psychiatry.* 160: 1125 - 1132.

# Promoting recovery in people with schizophrenia whose illness has not responded adequately to treatment (treatment resistance)

**Characteristics of included studies (previous guideline)**

| Study | Methods | Participants | Interventions | Outcomes | Notes |
|---|---|---|---|---|---|
| **Altamura 1999** | Allocation: randomised, computer-generated, blocks for each investigator 1:1, concealed from investigators.<br>Blindness: double, medication kits issues.<br>Duration: 14 weeks (preceded by screening phase, unspecified). | Diagnosis: schizophrenia, paranoid (DSM-IV).<br>N=28.<br>Sex: not stated.<br>Age: not stated.<br>Setting: not stated.<br>History: partial or non-responders to treatment according to preset criteria. | 1. Olanzapine: dose range 5-20mg, mean 12.4 SD 3.2mg/day. n=23.<br>2. Haloperidol: dose range 5-20mg, mean 12.3 SD 3.3mg/day. n=25. | Leaving study early<br>Other adverse events: COSTART list, weight change.<br><br>Unable to use-<br>Global state: CGI (no data)<br>Mental state: BPRS, SANS (no data)<br>Side effects: AIMS (no data) | |

| | | | | | |
|---|---|---|---|---|---|
| **Anand 1998** | Allocation: "randomised".<br>Blindness: double - no further details.<br>Duration: 12 weeks.<br>Multicentre. | Diagnosis: schizophrenia (DSM-IV).<br>N = 273.<br>Sex: 78 F, 195 M.<br>Age: mean 38.8 years.<br>History: treatment resistant.*<br>Setting: not stated. | 1. Risperidone: individual dose titration - week 1-4 up to 6 mg, then kept within a range of 2-15 mg, mean 8.3 mg/day. N = 135.<br>2. Clozapine: individual dose titration - week 1-4 up to 600 mg, then kept within a range of 200-900 mg, mean dose 597.5 mg/day. N = 138. | Leaving the study early, relapse.<br>Physiological monitoring (lab tests).<br>Mental state (PANSS, PAS, BPRS, CGI).<br>Adverse effects. | Raw scores of the rating scales not available.<br>Insufficient description of the dropouts - 101 participants in the risperidone group and 100 participants in the clozapine group completed the study.<br><br>*Treatment resistant: severe, chronic disease and poor response to previous neuroleptics (no period of good functioning for at least 24 months despite the use of two antipsychotics, current episode without significant improvement for at least 6 months despite the use of an antipsychotic equivalent to haloperidol 20 mg for at least 6 weeks, total BPRS at least 45, and CGI at least 4. |

| | | | | | |
|---|---|---|---|---|---|
| **Beuzen 1998/ Beasley 1999/ Tollefson 2001/ HGCF** | Allocation: "randomly allocated". Blindness: double - no further details. Statistical technique: last observation carried forward. Duration: 18 weeks (preceded by 2-9 days washout). Multicentre. | Diagnosis: schizophrenia (DSM-IV). N = 180. Sex: 65 F, 115 M. Age: mean 38.6 years (SD 10.6) range 18-70. History: onset age ~ 23 years, duration ill ~ 16 years, treatment resistant.* Setting: not stated. | 1. Olanzapine: individual dose titration 15-25 mg/day, mean 22.2 mg/day. N = 90. 2. Clozapine: initial dose of 25-200 mg day 1-8, individual dose thereafter 200-600 mg/day, mean 354.2 mg/day. N = 90. Benzodiazepine and chloral hydrate (agitation and insomnia), biperiden and benztropine mesylate (EPS) as required. | Leaving the study early. Physiological monitoring (vital signs, lab tests). Mental state (PANSS, BPRS, CGI). Adverse effects (dichotomous scale).<br><br>Unable to use: Extrapyramidal symptoms (Barnes, modified SAS, AIMS) - mean endpoint values and SDs not reported. | Abstracts only. Insufficient description of the dropouts - 107 participants completed the study: 60% in the olanzapine group, 58.9% in the clozapine group.<br><br>*Treatment resistant: lack of response to 2 antipsychotics of different class given at least 6 weeks at dose of at least 500 mg/day chlorpromazine equivalents or highest tolerated dose. BPRS(1-7) at least 45 and a score of at least 4 on at least 2 items on PANSS positive subscale (items 1-7). |

| | | | | | |
|---|---|---|---|---|---|
| **Bitter 1999** | Duration: 18 weeks<br>Washout: 2-9 days<br>Concomitant medications: Not stated<br><br>Comments: Numbers in each group not given | Age: most >30<br>Sex: 59.3% M<br>Illness: schizophrenia<br>Diagnosis: DSM-IV<br>N: 150<br>Duration of illness: Not stated.<br>Special characteristics: Treatment-resistant or -intolerant<br>Inclusion/ exclusion criteria:<br>Patients' symptoms must have failed to respond adequately to standard acceptable antipsychotic medication, either because of ineffectiveness or because of intolerable side effects caused by the medication. | Intervention:<br>Olanzapine<br>N: not stated<br>Dose:<br>10 mg/day<br><br>Control:<br>Clozapine<br>N: not stated<br>Dose: 25 mg/day, titrated in a fixed manner from 25 mg/day to 150 mg/day over 7 days. | Patients treated with olanzapine reported statistically more back pain and patients treated with clozapine reported statistically more somnolence and dizziness. Tachycardia occurred numerically more often in clozapine-treated versus olanzapine-treated participants. In terms of extrapyramidal symptoms, no statistically significant differences in parkinsonism (measured by Simpson-Angus scale), akathisia (measured by Hillside Akathisia scale) and dykinesia (measured by Abnormal Involuntary Movement Scale) were found. There was no statistically significant difference in weight change between clozapine and olanzapine treated participants. | Authors' conclusions:<br>Olanzapine demonstrated similar efficacy and safety to clozapine among participants with treatment-resistant schizophrenia. |

| | | | | | |
|---|---|---|---|---|---|
| **Bondolfi 1998** | Allocation: "randomly assigned", blocks of 4.<br>Blindness: double, "double-dummy" protocol.<br>Duration: 8 weeks (preceded by neuroleptic free period).<br>Multicentre. | Diagnosis: schizophrenia (DSM-III-R).<br>N=86<br>Sex: 25F, 61M.<br>Age: mean 37.3 years (SD 12.6).<br>History: moderate-severe illness, duration ill ~14 years, onset age ~26 years (SD 8.8), treatment resistant.*<br>Setting: hospital - week 1-3. | 1. Risperidone: individual dose titration - week 1, fixed dose thereafter 6mg/day - week 2, adjusted thereafter according to response, mean 6.4 mg/day, range 3-12 mg/day.<br>2. Clozapine: individual dose titration - week 1, fixed dose thereafter 300mg/day - week 2, adjusted thereafter according to response, mean 291 mg/day, range 150-400 mg/day.<br>Lorazepam and oxazepam (sleep induction), biperiden and procyclidine (EPS), clothiapine (emergency treatment) as required. | Leaving the study early.<br>Global state (CGI).<br>Mental state (PANSS).<br>Extrapyramidal symptoms (ESRS).<br>Other adverse events (UKU). | *Treatment resistant: failed to respond/ intolerant of >2 different classes of antipsychotics in appropriate doses for >4 weeks. |

| | | | | | |
|---|---|---|---|---|---|
| **Breier 1999** | Allocation: "randomly assigned".<br>Blindness: double - no further details.<br>Duration: 6 weeks (preceded by fluphenazine treatment for at least 2 weeks; then, 66% of the participants underwent a drug-free period, mean 18 days). | Diagnosis: schizophrenia (DSM-IV).<br>N = 29.<br>Sex: 10 F, 19 M.<br>Age: mean 35.0 years, range 18-55 years.<br>History: duration ill ~12.5 years, chronic schizophrenia, partial response to neuroleptics.*<br>Setting: not stated. | 1. Risperidone: gradual dose titration up to 6 mg - two weeks, adjustments over the next 2 weeks within fixed limits 2-9 mg/day, thereafter fixed dose, mean 5.9 mg/day. N = 15.<br>2. Clozapine: gradual dose titration up to 400 mg/day - 2 weeks, adjustments over the next two weeks within fixed limits 200-600 mg/day, thereafter fixed dose, mean 403.6 mg/day. N = 14.<br>benztropine mesylate (EPS) as required. | Leaving the study early.<br>Physiological monitoring (lab tests).<br>Mental state (BPRS, SANS, HDRS).<br>Extrapyramidal side effects (modified SAS). | No dropouts after randomisation phase.<br><br>*Partial response to neuroleptics: 1) a history of residual positive and/or negative symptoms after at least a 6-week trial of a therapeutic dose of a neuroleptic agent, 2) at least a minimum level of positive (four positive BPRS items at least eight) and/or negative (SANS score at least 20) symptoms at the time of evaluation for the study, and 3) at least a minimum level of positive and negative symptoms after a prospective trial of a least two weeks of fluphenazine 20 mg/day (range 10-30 mg/day). |

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| **Breier 2000** | Duration:<br>6 weeks | Age: not stated<br>Sex: not stated<br>Illness: schizophrenia<br>Diagnosis: not stated<br>N: 526<br>Duration of illness:<br>Special characteristics:<br>Subpopulation of treatment-resistant participants<br>Inclusion/ exclusion criteria: Not stated | Intervention:<br>Olanzapine<br>N: not stated<br>Dose:<br>Mean (SD) dose: 11.1 (3.4) mg/day<br><br>Control:<br>Haloperidol<br>N: not stated<br>Dose:<br>Mean (SD) dose: 10.0 (3.6) mg/day | Not reported | Authors' conclusions:<br>OLZ was superior to HAL for key symptom domains and parkinsonian adverse events. Implications of these data for the therapeutics of this severely ill subgroup are discussed.<br><br>Comments:<br>OLZ demonstrated significantly greater mean improvement from baseline on PANSS negative symptoms, comorbid depressive symptoms (MADRS), akathisia (Simpson-Angus SPS rating scale) with LOCF analysis.<br>OLZ was significantly superior to HAL for BPRS total (p=0.006), PANSS total (p=0.005) and PANSS positive (p=0.017) in completers.<br>Significantly greater response rates were observed in OLZ participants (47%) than HAL participants (35%) (p=0.008) in LOCF analysis. |

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| **Buchanan 1998** | Randomised.<br>Double-blind.<br>Duration: 10 weeks (no wash-out).<br>Setting: community. | Diagnosis: schizophrenia (DSM-III-R & SCID), chronic.<br>History: non-complete response to at least two trials of therapeutic doses of neuroleptics for at least 6 weeks. Less than 30% improvement in prospective 6 week trial of fluphenazine 10-30 mg/day.<br>N=75.<br>Sex: 23 female, 52 male.<br>Age: 18-55 years, mean 35 years. | 1) Clozapine pills: dose increased to 400mg/day week 1-4, 200-600 mg/day week 5-6, fixed dose week 7-10, average dose at study end 413 ±SD 60mg/day + placebo. n=38<br>2) Haloperidol pills: dose increased to 20 mg/day week 1-4, 10-30 mg/day week 5-6, fixed dose week 7-10, average dose at study end 26 ±SD 7 mg/day + benztropine 4 mg/day. n=37. | Relapse.<br>Clinical improvement: 20% reduction in BPRS (data not reported).<br>Acceptability: dropouts.<br>Mental state: 18-item BPRS, SANS.<br>Quality of life: QOLS<br>Global functioning: Level of Functioning Scale<br>Adverse effects: SAI, Maryland Psychiatric Research Centre Involuntary Movement Scale.<br>Compliance. | Jadad[2] score 4.<br>Drop-outs (n=2) excluded from results in original report have been included in present meta-analysis.<br>Benztropine medication in group 2 may have affected results. |
| **Chowdhury 1999** | Duration:<br>16 weeks<br>Washout:<br>7 day<br>Concomitant medications:<br>None reported. | Age: Mean (SD):CL 30.3 (8.78) years; RI 32.43 (9.79) years<br>Sex: CL22/30 M; RI 23/30 M<br>Illness: schizophrenia<br>Diagnosis: ICD10<br>N: 60<br>Duration of illness: Mean (SD): CL 6.92 (5.07) years; 18 (4.38) years<br>Special characteristics: Clozapine: paranoid | Intervention:<br>Clozapine<br>N: 30<br>Dose:<br>Initial dose 50 mg/day, increased by 50 mg to 150 mg/day by week 2. By week 3, dose range 250-300 mg/day.<br><br>Control:<br>Risperidone<br>N: 30<br>Dose: 1mg x2 daily | Intervention group:<br>6 dropouts: 4 side effects; 1 refusal to do blood test; 1 lost to follow-up<br>8 dropouts: 3 severe akathisia; 3 inadequate response; 2 lost to follow-up<br><br>Clozapine: tachycardia 76.66%; hypersalivation 60%; sedation 60%; weight gain 43.33%; constipation 30%; | Authors' conclusions:<br>Both clozapine and risperidone were effective and well tolerated at standard doses in Indian participants with chronic schizophrenia who had been resistant to or intolerant of conventional neuroleptics.<br><br>Comments:<br>Results of statistical analyses reported in paper very unclear. |

[2] JADAD scores relate to a quality assessment scale: the JADAD scale (Jadad, A.R., Moore, R.A., Carroll, D. *et al.* (1996) Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Controlled Clinical Trials, 17,* 1–12). The JADAD scale has not been applied to any papers in the update, instead the SIGN checklist has been applied.

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| | | subtype 56.67%<br>Risperidone: paranoid subtype 60%<br>Other subtypes included hebephrenia, residual and undifferentiated.<br>Inclusion/exclusion criteria:<br>Aged 15-60 years; duration of illness > 6 months and received at least one full course of treatment with conventional antipsychotics (either chlorpromazine 600-800 mg/day, haloperidol or trifluoperazine in equivalent doses) without adequate response; cases intolerant to traditional neuroleptics because of intractable neurological and non-neurological side effects necessitating withdrawal of drug or inadequate dosing.<br>Further details: 72 participants satisfied the inclusion criteria for the study, 9 participants did not enter the trial.<br>Among the 63 remaining participants, 3 dropped out during the wash-out period. | starting dose then 2mg x2 daily from day 2 onwards. After week 1, 6mg/day up to max 8mg/day.<br><br>The mean (SD) maximum dose of clozapine was 342.86 (84.21) mg/day and for risperidone it was 5.8 (1.33) mg/day. | leucocytosis 26.66%. (1 patient experienced a seizure)<br>Risperidone: constipation 50%; dry mouth 46.66%; weight gain 43.33%; akathisia 36.67%; insomnia 33.33%; tachycardia 30%; impotence 26.66%. | |

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| **Claghorn 1987** | Randomised.<br>Double-blind (identical tablets).<br>Multi-centre.<br>Duration: 4-8 weeks (preceded by 2 weeks wash-out).<br>Setting: hospital. | Diagnosis: schizophrenia (DSM-II).<br>History: Intolerant to at least two prior neuroleptics.<br>N=151.<br>Sex: 59 female, 92 male.<br>Age: 18-65 years, median 30 years. | 1) Clozapine tablets: initial dose 25 mg/day; 1-week build-up to 300 mg/day. Day 8-28: dose 150-900 mg/day, average 417 mg/day. n=75.<br><br>2) Chlorpromazine tablets: initial dose 50 mg/day; 1-week build-up to 600 mg/day. Day 8-28: dose 300-1800 mg/day, average 795 mg/day. n=76.<br>Fixed-flexible dose schedule. | Relapse.<br>Global effect: CGI.<br>Acceptability: drop-outs.<br>Mental state: 18-item BPRS.<br>Behaviour: 30-item NOSIE.<br>Adverse effects: AIMS, SAS (not blind). | |

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| **Conley 1998a** | Allocation: randomised - no further details.<br>Blindness: double.<br>Duration: 8 weeks (preceded by 6/52 weeks of haloperidol & 1-2/52 washout).<br>Investigators: trained on BPRS & SANS. | Diagnosis: schizophrenia (DSM-III-R).<br>Inclusion criteria: minimum BPRS score of 45, CGI-S score >3, treatment resistant, non-responders during haloperidol phase.<br>Multicentre: 3 sites.<br>Sex: 62 M, 22 F.<br>Setting: in hospital. | 1. Olanzapine: dose 25mg/day. n=42.<br><br>2. Chlorpromazine: dose 1200mg/day & benztropine 4mg/day. n=42.<br>Allowed benzodiazepine during washout & first 3/52 of trial. | Global state (CGI).<br>Mental State (BPRS*, SANS).<br>Leaving study early.<br>Side effects (Barnes Akathisia Scale, SAS).<br><br>Unable to use - Behaviour - use of benzodiazepines (no data).<br>Hospital status (no data).<br>Lab tests & physiological measures (no data). | *A priori efficacy >19 decrease from baseline or to <34 total score.<br>Treatment resistance defined as: 1. At least two periods of treatment in the preceding 5 years with an antipsychotic drug (from at least two different classes, excluding haloperidol) at dosages greater or equal to 1000mg of chlorpromazine daily for 6 weeks without significant symptomatic relief;<br>2. No period of good functioning within the past five years; and<br>3. Severity of psychopathology indicated by a BPRS total score greater or equal to 45, a CGI severity score greater or equal to 4, and a score of greater or equal to 4 on at least two of the BPRS psychosis items. |

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| **Emsley 1999** (Multi-country 1999) | Allocation: randomised, no further details.<br>Blindness: double-blind, no further details.<br>Duration: 8 weeks (preceded by a 4 week washout period with all participants on fluphenazine 20 mg/day and only participants who met inclusion criteria after this were included) | Diagnosis: schizophrenia (DSM-IV).<br>Inclusion criteria: persistent positive symptoms whilst previously taking antipsychotics, PANSS (P) >=15, CGI >=3. N=288.<br>Age: mean 39 years<br>Sex: M 203, F 85 | Quetiapine 600mg/day, n=143.<br>Haloperidol 20mg/day. n=145 | Global state (CGI)<br>Mental state (PANSS)<br>Mental state - specific positive symptoms PANNS positive scale<br>Mental state - specific negative symptoms PANSS negative scale<br>Mental sate - specific mood derived BPRS mood cluster<br>Side effects - modified Simpson-Angus<br>Side effects - need for anticholinergic medication<br>Leaving the study early. | |

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| **Heck 2000** | Duration:<br>6 weeks + 1 week dose-rising phase<br>Washout:<br>none<br>Concomitant medications:<br>All antiparkinsonian drugs and psychotropic drugs except benzodiazepines were stopped. If a participant developed EPS during the trial, antiparkinsonian drugs were permitted. Psychotropic drugs, except benzodiazepines, were not allowed.<br><br>Comments:<br>Dose rising phase was one week: day 1, one tablet; day 2, 2 tablets; days 3-7, 3 tablets | Age: Mean R 40 years, H 44.5 yrs (range 23-68)<br>Sex: 38 M, 39 F<br>Illness: combined diagnoses<br>Diagnosis: DSM-III-R<br>N: 77<br>Duration of illness:<br>?14 years<br>Special characteristics:<br>schizophrenia (subchronic or chronic course) or other psychotic conditions. Participants who had disturbing EPS during their previous neuroleptic treatment.<br>Inclusion/ exclusion criteria:<br>18-70 years, clinically stable on current antipsychotic medication, score of at least 5 on the subscale parkinsonism on the ESRS, or using antiparkinsonian medication.<br>Further details:<br>Hospitalised, average duration 7 years. | Intervention:<br>risperidone<br>N: 40<br>Dose:<br>flexible dose (max 16mg)<br>oral<br><br>Control:<br>haloperidol<br>N: 37<br>Dose:<br>flexible dose (max 24mg)<br>oral<br><br>Intervention group n:<br>15/40 withdrew (reasons not stated)<br><br>Control group n:<br>15/37 withdrew (reasons not stated) | Overall frequency of adverse events was similar in the two treatment groups. In the risperidone group the most frequent AEs were headache (4/40), oculogyric crisis (3/40) and hypersalivation (3/40). In the haloperidol group the most frequent AEs were sleep disorders (4/37), tremor (4/37) and vomiting (3/37). Five participants in the risperidone group and six in the haloperidol group stopped medication because of AEs. | |

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| **Hong 1997** | Randomised.<br>Double-blind.<br>Duration: 12 weeks (preceded by a 60 mg/day haloperidol baseline period lasting up to 6 weeks)<br>Setting: hospital. | Diagnosis: schizophrenia (DSM-IV).<br>History: treatment-refractory*<br>N=40.<br>Sex: 26 female, 14 male.<br>Age: clozapine 40 ±8 years, chlorpromazine 37 ±9 years. | 1) Clozapine capsules: initial dose 25 mg/day for 1 week, mean dose 543 ±157 mg/day. Max dose 900 mg/day. n=21.<br>2) Chlorpromazine capsules: initial dose 50 mg/day for 1 week, mean dose 1163 ±228 mg/day. Max dose 1800 mg/day. n=19.<br>Fixed-flexible dose schedule. | Acceptability: drop-outs.<br>Mental state: PANSS, BPRS.<br>Global effect: CGI.<br>Improvement: decrease at least 20% in BPRS total score.<br>Adverse effects. | *Treatment refractory= Severe psychotic symptoms according to BPRS item scores for >6 months despite treatment with neuroleptics from at least two different classes at dosages of at least 1000 mg chlorpromazine equivalents. |
| **Kane 1988** | Randomised.<br>Multi-centre.<br>Double-blind.<br>Duration:6 weeks.<br>Setting: hospital. | Diagnosis: schizophrenia (DSM-III), undifferentiated ~50%, paranoid ~33%.<br>History: treatment-resistant*, unresponsive/ intolerant to 6 weeks haloperidol and benztropine period.<br>N=268.<br>Sex: 20% female, 80% male.<br>Age: average - clozapine 36 (SD 9), chlorpromazine 36 (SD 8) years. | 1) Clozapine capsules: dose up to 500 mg/day week 1-2, flexible dose thereafter, max 900 mg/day. n=126.<br>2) Chlorpromazine capsules: dose up to 1000 mg/day week 1-2, flexible dose thereafter, max 1800 mg/day. Also benztropine 6mg/day. n=142. | Death.<br>Relapse.<br>Acceptability: drop-outs.<br>Improvement: decrease of > 20% in BPRS total score & CGI score of <3 or BPRS total score < 35.<br>Global effect: CGI.<br>Mental state: BPRS.<br>Behaviour: NOSIE.<br>Adverse effects: AIMS, SAS. | * Treatment resistant = 3+ periods of neuroleptic treatment, 1000 mg/day of CHL equivalents without significant symptomatic relief and BPRS total score of at least 45. |

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| **Kern 1998** | Duration:<br>8 weeks<br>Washout:<br>placebo washout: 3-7 days<br>Concomitant medications:<br>As required: lorazepam or chloral hydrate. Benztropine mesylate or propanolol were administered at the discretion of the treating psychiatrist. On three occasions biperiden hydrochloride was substituted for benztropine mesylate.<br><br>Comments:<br>At site 1, participants received 15-30 mg/day of haloperidol for 3 weeks before washout. At site 2, the baseline phase consisted of an 'off-medication', 'lead-in phase' of which the duration is not stated. | Age: Mean (SD): H 39.6 (7.8); R 40.8 (10.2)<br>Sex: M:F H 25:4; R 20:7<br>Illness: schizophrenia<br>Diagnosis: DSM-III-R<br>N: 56<br>Duration of illness:<br>Mean (SD): H 18.5 (7.9) years; R 19.2 (10.0) years<br>Special characteristics:<br>All participants included in the study were considered treatment resistant according to the criteria of Kane et al (1988).<br>Inclusion/ exclusion criteria:<br>Inclusion: Met the symptom severity and exclusionary criteria at the time of the initial screening (see Green at al 1997b).<br>Further details:<br>BPRS total scores at baseline: H 67.8 (12.0); R 63.8 (10.6)<br>thinking disturbance: H 13.4 (3.2); R 12.6 (3.4)<br>withdrawal/retardation: H 8.4 (3.0); 8.5 (3.2)<br>EPS scores (SAS): H 3.1 (4.2); R 3.1 (5.2). | Intervention:<br>Risperidone<br>N: 27<br>Dose:<br>6 mg/day for 4 weeks flexible dose for following 4 weeks (mean = 7mg/day)<br><br>Control:<br>Haloperidol<br>N: 29<br>Dose:<br>15 mg/day for 4 weeks flexible dose for following 4 weeks (mean = 19mg/day) | None reported. | |

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| **Klieser 1989** | Double blind.<br>Duration: 6 weeks (preceded by 14 day washout).<br>Setting: hospital. | Diagnosis: schizophrenia - chronic treatment-resistant (no diagnostic criteria).<br>N=32.<br>Sex: 19 female, 11 male.<br>History: duration of illness average 17 (SD 8) years.<br>People on depot medication excluded.<br>Age: average - 48 (SD 11) years | 1) Clozapine: dose 400mg/day. n=16.<br>2) Haloperidol: dose 20mg/day. n=16.<br>Biperiden and chloral hydrate as needed. | Relapse.<br>Acceptability: dropouts.<br>Global effect: CGI.<br>Mental state: BPRS, AMDP and SANS. | |
| **Meyer-Lindberg 1996** | Allocation: random - no further details.<br>Blinding: double - no further details.<br>Duration: 6 weeks. | Diagnosis: schizophrenia (DSM-III-R).<br>N=50.<br>Age: mean ~ 33 years (SD~10).<br>Sex: male 18 (only describe those they report on).<br>History: unresponsive to > 3 weeks of 2 typical antipsychotics in effective doses, BPRS >39. | 1. Zotepine: dose 150-450mg/day. n=25<br>2. Clozapine: dose 150-450mg/day. n=25. | Leaving the study early.<br><br>Unable to use -<br>Global function (CGI - no mean or SD).<br>Mental State (BPRS, SANS - no mean or SD).<br>Behaviour (CIPS [Collegium Internationale Psychiatriae Scalarum], NOSIE - no mean or SD)<br>Side effects (UKU).<br>Cognitive function (maze tests - no mean or SD).<br>ECG (no data).<br>Weight gain (no data). | |

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| **Oliemeulen 2000** | Duration:<br>8 weeks | Age: not stated<br>Sex: not stated<br>Illness: combined diagnoses<br>Diagnosis: DSM-IV<br>N: 36<br>Duration of illness: Not stated<br>Inclusion/ exclusion criteria:<br>Therapy-resistant; schizophrenia or other psychotic disorders | Intervention:<br>Olanzapine<br>N: 21<br>Dose:<br>Not stated<br><br>Control:<br>Clozapine<br>N: 15<br>Dose:<br>Not stated | None reported. | |
| **Rosenheck 1997** | Randomised.<br>Double-blind: placebo benztropine given to clozapine group, blood counts taken from haloperidol group.<br>Multi-centre.<br>Duration: 1 year.<br>Setting: Hospital and outpatient services. | Diagnosis: schizophrenia (DSM III-R & SCID).<br>History: mean age onset 22 years, treatment-resistant, high level use of inpatient services (30-364 days of hospitalisation in preceding year.<br>N=423.<br>Sex: 10 female, 413 male.<br>Age: clozapine group mean 43 (SD 8) years, haloperidol group mean 44 (SD 8) years. | 1) Clozapine: flexible dose 100-900 mg/day, average dose at week 26: 552 ±SD 229 mg/day. n=205.<br><br>2) Haloperidol: flexible dose 5-30 mg/day, average dose at week 26: 28 ±SD 5.3 mg/day. Also benztropine 2-10 mg/day. n=218. | Acceptability: dropouts.<br>Mental state: PANSS.<br>Improvement: decrease of >20% in PANSS total.<br>Quality of life: Heinrichs-Carpenter Quality of Life Scale.<br>Adverse effects: AIMS, Barnes Akathisia Scale, Simpson-Angus Scale, adverse effects checklist.<br>Use of services: days of hospitalisation (skewed data), outpatient visits (no SD given).<br>Costs: medication, health care, estimated non-healthcare costs. | |

**References of included studies (previous guideline)**

**Altamura 1999**

Altamura, A.C., Velona, I., Curreli, R., Bravi, D. (1999). Olanzapine in the treatment of paranoid schizophrenia. *European Neuropsychopharmacology, 9(suppl 5),* S297.

**Anand 1998**

Anand R, Alphs L, Azorin JM, Remington G, Pere JJ, Bourdeix I. (1998) Superior efficacy of clozapine in chronic severe schizophrenia: comparison with risperidone. Highlights. *Journal of Clinical Psychiatry*; 60(suppl 12):3-50.

**Beuzen 1998/Beasley 1999/ Beasley 1999/ Tollefson 2001/ HGCF**

Beasley CM, Beuzen JN, Birkett MA, Kiesler GM, Tollefson GD, Wood AJ. (1999) Olanzapine versus clozapine: an international double-blind study of the treatment of resistant schizophrenia. In: *152nd Annual Meeting of the American Psychiatric Association*; 15 - 20 May 1999; Washington DC, USA

Eli Lilly and Company Limited (2001) The use of the newer (atypical) antipsychotics in the treatment of schizophrenia: Olanzapine. Submission to: the National Institute for Clinical Excellence. Basingstoke: Eli Lilly and Company Limited, 1 June 2001.

**Bitter 1999**

Bitter I, Brook S, Dossenbach M, Janka Z, Banki CM, Selemani S, et al. (1999) Olanzapine versus clozapine in patients non-responsive or intolerant to standard acceptable treatment of schizophrenia. *European Neuropsychopharmacology*; 9(suppl. 5):S288-S289.

**Bondolfi 1998**

Bondolfi G, Dufour H, Patris M, May JP, Billeter U, Eap CB, et al. (1998) Risperidone versus clozapine in treatment-resistant chronic schizophrenia: a randomised double-blind study. *American Journal of Psychiatry*; 155(4):499-504.

**Breier 1999**

Breier AF, Malhotra AK, Su TP, Pinals DA, Elman I, Adler CM, et al. (1999) Clozapine and risperidone in chronic schizophrenia: effects on symptoms, parkinsonian side effects, and neuroendocrine response. *American Journal of Psychiatry*; 156(2):294-8.

**Breier 2000**

Breier A, Hamilton SH. (2000) Comparative efficacy of olanzapine and haloperidol for patients with treatment-resistant schizophrenia. *Schizophrenia Research*; 41(1):188.

Breier A, Hamilton SH. (1999) Comparative efficacy of olanzapine and haloperidol for patients with treatment-resistant schizophrenia. *Biological Psychiatry*; 45(4):403-11.

**Buchanan 1998**

Buchanan RW, Breier A, Kirkpatrick B, Ball P, Carpenter WT. (1998) Positive and negative symptom response to clozapine in schizophrenic patients with and without the deficit syndrome. *American Journal of Psychiatry*; 155(6):751-760.

Baymiller,S.P.; Ball,P.; McMahon,R.P.; Buchanan,R.W. (2002) Weight and blood pressure change during clozapine treatment. *Clinical Neuropharmacology.* 25(**4**): 202 - 206.

**Chowdhury 1999**

Chowdhury AN, Mukherjee A, Ghosh K, Chowdhury S, Das Sen K. (1999) Horizon of a new hope: Recovery of schizophrenia in India. *International Medical Journal*; 6 (3):181-185.

**Claghorn 1987**

Claghorn J, Honigfeld G, Abuzzahab FS, Wang R, Steinbook R, Tuason V, et al. (1987) The risks and benefits of clozapine versus chlorpromazine. *Journal of Clinical Psychopharmacology*; 7:377-84.

**Conley 1998**

Conley RR, Tamminga CA, Bartko JJ, Richardson C, Peszke M, Lingle J, et al. (1998) Olanzapine compared with chlorpromazine in treatment-resistant schizophrenia. *American Journal of Psychiatry*; 155(7):914-920.

**Emsley 1999 (Multi-country 1999)**

Emsley RA, Raniwalla J, Bailey PJ, Jones AM. (2000) A comparison of the effects of quetiapine ('Seroquel') and haloperidol in schizophrenic patients with a history of and a demonstrated, partial response to conventional antipsychotic treatment. *International Clinical Psychopharmacology*;15:121-131.

Buckley,P.F.; Goldstein,J.M.; Emsley,R.A. (2004) Efficacy and tolerability of quetiapine in poorly responsive, chronic schizophrenia. *Schizophrenia Research.* 66: 143 - 150.

Emsley,R.A.; Buckley,P.; Jones,A.M.; Greenwood,M.R. (2003) Differential effect of quetiapine on depressive symptoms in patients with partially responsive schizophrenia. *Journal of Psychopharmacology* 17: 210 - 215.

**Heck 2000**

Heck AH, Haffmans PMJ, De Groot IW, Hoencamp E. (2000) Risperidone versus haloperidol in psychotic patients with disturbing neuroleptic-induced extrapyramidal symptoms: A double-blind, multi-center trial. *Schizophrenia Research*; 46(2-3):97-105.

**Hong 1997**

Hong CJ, Chen JY, Sim CB. (1997) A double-blind comparative study of clozapine versus chlorpromazine on Chinese patients with treatment-refractory schizophrenia. *International Clinical Psychopharmacology;* 12(3):123-130.

**Kane 1988**

Kane JM, Honigfeld G, Singer J, Meltzer H. (1988) Clozapine in treatment-resistant schizophrenics. *Psychopharmacology Bulletin*; 24(1):62-67.

**Kern 1998**

Kern RS, Green MF, Marshall BD, Wirshing WC, Wirshing D, McGurk S, et al. (1998) Risperidone vs. haloperidol on reaction time, manual dexterity, and motor learning in treatment-resistant schizophrenia patients. *Biological Psychiatry*; 44(8):726-32.

McGurk,S.R.; Green,M.F.; Wirshing,W.C.; Wirshing,D.A.; Marder,S.R.; Mintz,J.; Kern,R. (2004) Antipsychotic and anticholinergic effects on two types of spatial memory in schizophrenia. *Schizophrenia Research.* 68(**2-3**): 225 - 233.

**Klieser 1989**

Klieser E, Schonell H. (1990) Klinisch-pharmakologische Studien zur Behandlung schizophrener Minussymptomatik. In: Moller HJ, Pelzer E, eds. *Neuere Ansatze zur Diagnostik und Therapie schizophrener Minussymptomatik*. Berlin: Springer-Verlag.

**Meyer-Lindenberg 1996**

Meyer-Lindenberg A, Bauer U, Lis S, Krieger S, Gallhofer B. (1997) Improvement of cognitive function in schizophrenic patients receiving clozapine or zotepine: Results from a double-blind study. *Pharmacopsychiatry*; 30(2):35-42.

**Oliemeulen 2000**

Oliemeulen EAP, van Hoof JJM, Jogems-Kosterman BJM, Hulstijn W, Tuynman-Qua HG. (2000) Is olanzapine a substitute for clozapine? The effects on psychomotor performance. *Schizophrenia Research*; 41(1):187.

**Rosenheck 1997**

Rosenheck R, Cramer J, Weichun XU, Thomas J, Henderson W, Frisman L, et al. (1997) A comparison of clozapine and haloperidol in hospitalised patients with refractory schizophrenia. *New England Journal of Medicine*; 337:809-15.

**Characteristics of included studies (update)**

| **Study ID** | **BUCHANAN2005** |
|---|---|
| **General info** | **Funding source:** Non-industry support |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** ITT - Not specifically stated, but appears to have been taken into account in analyses |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment 16 |
| | **Raters:** Not stated to be independent of treatment |
| | **Design:** Single-centre - Maryland, US |
| | **Number of people screened, excluded & reasons:** 68 entered open-label fluphenazine evaluation phase, 63 completed and showed no response to fluphenazine, and randomised for double-blind phase |
| | **Notes about study methods:** Randomisation procedures not reported |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 100% schizophrenia or schizoaffective |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:**<br>- DSM-IV schizophrenia or schizoaffective disorder<br>- Showed partial response to fluphenazine during 4-week open-label phase: demonstrated <30% improvement in positive and negative symptoms, met minimal level of positive and negative symptom criteria, or intolerant of fluphenazine |
| | **Exclusion criteria:**<br>- Concurrent drug abuse or alcoholism<br>- Organic brain disorders<br>- Mental retardation |
| | **Total sample size:** ITT population 63 |
| | **Total sample size:** No. randomised 63 |
| | **Gender:** % female 26% |
| | **Age:** Mean<br>Olanzapine: 41.9 (7.0) |

Haloperidol: 46.4 (9.0)

**Ethnicity:**
African American 46%
Caucasian 54%

**Setting:** Outpatient

**History:**
[Olanzapine / Haloperidol]
Age of onset: 21.4 (6.6) / 24.6 (7.5)
Years of illness: 20.5 (6.3) / 21.7 (10.1)

**Baseline stats:**
[Olanzapine / Haloperidol]
BPRS: 35.5 (9.1) / 34.7 (8.8)
SANS: 30.6 (10.8) / 30.0 (10.6)

**Interventions**

**Intervention - group 1.:** Olanzapine, n=29

**Intervention - group 2.:** Haloperidol, n=34

**Notes about the interventions:**
Olanzapine and haloperidol initiated at 15/mg day; fluphenazine was gradually tapered off over first 2 weeks. Study medication dose was titrated between 10-30mg/day to maximise efficacy or minimise side effects.

Benztropine (adjusted between 0-6mg/day) was prescribed for the haloperidol group to minimise EPS and the potential for revealing treatment assignment. Olanzapine group were given placebo benztropine.

**Outcomes**

**Global state & service outcomes (e.g. CGI):** Average score/change in global state - CGI

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - BPRS, SANS, HAM-D

**General and psychosocial functioning (e.g. SFS):** Average score/change in general functioning - Level of Functioning Scale

**Adverse events:** Average score/change in specific adverse effects - SAS, Maryland TD Scale

**Adverse events:** Average score/change in general adverse effects - Side Effects Checklist

**Quality of Life:** Average score/change in quality of life - QoL score

**Other:** BP, pulse, weight

**Quality**

**1.1 The study addresses an appropriate and clearly focused question.:** Well covered

**1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately

**1.3 An adequate concealment method is used.:** Not addressed

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered

**1.5 The treatment and control groups are similar at the start of the trial.:** Well covered

**1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** <20%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Well covered

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not applicable

**2.1 How well was the study done to minimise bias?:** +

| **Study ID** | **CONLEY2005** |
|---|---|
| **General info** | **Funding source:** Non-industry support |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment 12 |
| | **Raters:** Not stated to be independent of treatment |
| | **Design:** Single-centre - US |
| | **Number of people screened, excluded & reasons:** 52 began open-label phase, 40 subsequently eligible and gave consent and randomised, 2 records lost therefore 38 included in final analysis |
| | **Notes about study methods:** Randomisation procedures not reported |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 100% |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:**<br>- Aged 18-65<br>- Met DSM-IV criteria for schizophrenia<br>Treatment resistant as defined by:<br>- Persistent positive symptoms (>=4 points on 2 of 4 BPRS psychosis items) |

- Persistent global illness severity (BPRS Total >=45 and CGI >=4)
- At least two prior failed treatment trials with two different antipsychotics at doses of >=600mg/day chlorpromazine equivalent each of at least 6 weeks duration
- No stable period of good social/occupational functioning in past 5 years.

Following lead-in phase, patients not achieving 20% reduction in BPRS and where BPRS >=35 and CGI >=4 were randomised into the double-blind phase of the study.

**Total sample size:** No. randomised 40

**Total sample size:** Safety population 37

**Total sample size:** ITT population 38

**Gender:** % female 21%

**Age:** Mean
Risperidone: 46.3 (8.7)
Quetiapine: 43.7 (5.9)
Fluphenazine: 44.2 (8.8)

**Ethnicity:** Black 53%

**Setting:** Inpatient

**History:**
[Risperidone / Quetiapine / Fluphenazine]
Previous hospitalisations: 14.0 (10.8) / 9.7 (5.3) / 12.0 (5.2)

**Baseline stats:**
[Risperidone / Quetiapine / Fluphenazine]
BPRS: 56.00 (14.08) / 53.30 (7.37) / 54.69 (13.67)

**Notes about participants:** All participants underwent a 4-6 week open-label lead-in phase with either olanzapine, or a typical antipsychotic other than fluphenazine.

**Interventions**

**Intervention - group 1.:** Risperidone, 4mg/day, n=13

**Intervention - group 2.:** Quetiapine, 400mg/day, n=12

**Intervention - group 3.:** Fluphenazine, 12.5mg/day, n=13

**Notes about the interventions:**
Patients were titrated to the target dose during the first week, and clinicians had to option of adjusting daily dose of risperidone from 3-5mg/day, quetiapine 300-500mg/day, or fluphenazine 10-15mg/day if there were significant side effects or lack of efficacy after 6 weeks on fixed dose.

| | |
|---|---|
| | Routine concomitant psychotropic medications (such as antidepressants and mood stabilisers) were not allowed. Patients experiencing agitation or anxiety were allowed up to 10mg/day lorazepam as needed. Benztropine mesylate (up to 4mg/day) and propranolol (30-120mg/day) were given if needed for EPS. |
| **Outcomes** | **Leaving the study early:** Leaving because of adverse effects |
| | **Leaving the study early:** Leaving due to any reason (non-adherence to study protocol) |
| | **Global state & service outcomes (e.g. CGI):** Average score/change in global state - CGI-S |
| | **Global state & service outcomes (e.g. CGI):** Clinically significant response in global state - Response defined as >=20% decrease in BPRS; more stringent criteria also required CGI <=3. |
| | **Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - BPRS |
| | **Adverse events:** Number of people with specific adverse effects Use of adjunct medications, various AEs (anticholinergic, gastrointestinal, CNS, other) |
| | **Adverse events:** Average score/change in specific adverse effects - Weight |
| | **Quality of Life:** Average score/change in quality of life - QoL Interview |
| **Quality** | **1.1 The study addresses an appropriate and clearly focused question.:** Well covered |
| | **1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately |
| | **1.3 An adequate concealment method is used.:** Not addressed |
| | **1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Adequately addressed |
| | **1.5 The treatment and control groups are similar at the start of the trial.:** Well covered |
| | **1.6 The only difference between groups is the treatment under investigation.:** Well covered |
| | **1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered |
| | **1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** 20-50% |
| | **1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Well covered |
| | **1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not applicable |
| | **2.1 How well was the study done to minimise bias?:** + |

| Study ID | KANE2007B |
|---|---|
| General info | **Funding source:** Pharmaceutical industry |
| | **Published or unpublished data?:** Published |
| Method | **Type of study:** Individual randomised trial |
| | **Type of analysis:** ITT - All patients in the safety sample with at least 1 post-randomisation efficacy evaluation.<br>(safety sample defined as all randomised participants who took at least one dose of study medication.) |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment Double-blind trial was 6 weeks in duration |
| | **Raters:** Not stated to be independent of treatment |
| | **Design:** Multi-centre 59 centres throughout US and Canada |
| | **Number of people screened, excluded & reasons:** 512 patients underwent screening, of these 416 entered the open-label treatment phase. The open label treatment phase was used to confirm treatment resistant status, with only those who completed this period and failed to respond to treatment being allowed to proceed with the study.<br><br>334 (80%) completed the 6-week study with only 9 (2%) discontinuing due to showing a response to treatment.<br><br>In total 300 patients entered the double-blind phase, with 3 patients being excluded from the safety analysis and a further 3 from the efficacy analysis. |
| | **Notes about study methods:** Randomisation procedure not reported |
| Participants | **Diagnosis:** Schizophrenia [% of sample] 100% |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:**<br>- aged >18 years with a diagnosis of schizophrenia and classified as being treatment resistant (defined as failure to experience satisfactory symptom relief despite at least 2 periods of treatment, each lasting >=6 weeks with adequate doses of antipsychotics).<br>- patients should not have experienced satisfactory symptom relief with their most recent course of antipsychotic therapy<br>- PANSS score >=75 and a score >=4 on at least 2 items of conceptual disorganisation, suspiciousness, hallucinatory behaviour, or delusions.<br>- CGI-S score >=4<br>- Treated as an outpatient for at least 1 continuous 3-month period during the 2 years prior to entry. |
| | **Exclusion criteria:**<br>- DSM-IV diagnosis of schizoaffective disorder, residual schizophrenia or bipolar disorder<br>- clinical presentation or history of delirium, dementia, amnesic or other cognitive disorder |

- refractory response to prior clozapine treatment administered at therapeutic doses for 6 weeks or previous unresponsiveness to perphenazine
- likelihood to require prohibited concomitant therapy during the trial
- current or recent psychoactive drug or alcohol abuse or dependence
- history of suicidal attempts or serious suicidal thoughts
- known allergy or hypersensitivity to study drug
- treatment with an investigational drug within 4 weeks of the washout phase or previous enrolment in an aripiprazole study
- any other acute or unstable medical condition
- pregnant of lactating females.

**Total sample size:** No. randomised 300

**Total sample size:** Safety population 297

**Total sample size:** ITT population 294

**Gender:** % female 31%

**Age:** Mean 42.10(0.7)

**Ethnicity:** White - 50%
Black - 24%
Asian / Pacific islander - 3%
Hispanic/Latino - 19%
Other - 5%

**Setting:** Inpatient

**Setting:** Outpatient

**History:**
[Aripiprazole / Perphenazine]
Age at time of first hospitalisation: 22.6(0.5) / 22.9(0.7)

**Baseline stats:**
[Aripiprazole / Perphenazine]
PANSS total: 97.5 / 99.5
BPRS core score: 17.2 / 17.6
CGI-S: 5.0 / 5.0

**Interventions**

**Intervention - group 1.:** Aripiprazole, 15-30 mg/d, n=154

**Intervention - group 2.:** Perphenazine, 8-64mg/d, n=146

**Notes about the interventions:**
Aripiprazole

- started at 15mg/d and dose adjustment could be made to 30mg/d at the end of week 1.

Perphenazine
- started at 8mg/d and could be increased to 16mg/d on day 4 if needed. At the end of week 1, additional increases in perphenazine dose (in 8mg/d increments) could be made at 4- to 7-day intervals up to total of 64mg/d. Perphenazine doses greater than 8mg were administered twice daily.

For both drugs incremental dose reductions were permitted during the study provided patients remained within the permitted dose ranges.

General procedure:
All enrolled patients were subject to a 2-24 day screening period including minimum 2-day washout.
- participants underwent 4-6 week open-label treatment with either olanzapine or risperidone to confirm treatment resistant status.
- Those participants who did not respond (response defined as a reduction in PANSS >=20% and a CGI-S score 1-3)during the open label phase then entered the double-blind study.
- prior to start of the double-blind phase participants entered a single-blind placebo washout period lasting 2-10 days.

**Outcomes**

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Leaving the study early:** Leaving because of adverse effects

**Global state & service outcomes (e.g. CGI):** Clinically significant response in global state - Response defined as CGI-I score 1-2

**Global state & service outcomes (e.g. CGI):** Average score/change in global state - CGI

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS, BPRS

**Mental state (e.g. BPRS, PANSS, BDI):** Clinically significant response in mental state - Response defined as >=30% decrease in PANSS total score

**Adverse events:** Number of people with general adverse effects

**Adverse events:** Number of people with specific adverse effects. Table reporting all AEs experienced by >=5% of patients in either treatment group

**Adverse events:** Average score/change in specific adverse effects- SAS, AIMS, BAS

**Quality of Life:** Average score/change in quality of life - QLS

**Quality of Life:** Clinically important change in quality of life Clinically important improvement defined as >=20% improvement in QLS total score

**Other:** Prolactin, ECG, BMI and vital signs and laboratory parameters.

**Quality**

**1.1 The study addresses an appropriate and clearly focused question.:** Well covered

**1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately

**1.3 An adequate concealment method is used.:** Not addressed

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered

**1.5 The treatment and control groups are similar at the start of the trial.:** Well covered

**1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Well covered

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Adequately addressed

**2.1 How well was the study done to minimise bias?:** +

| **Study ID** | **KINON2006A** |
|---|---|
| **General info** | **Funding source:** Pharmaceutical industry |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** ITT - All participants with at least one post-baseline observation<br>Analysis for missing data using LOCF and mixed-effects repeated measures |
| | **Type of analysis:** LOCF |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment 24 |
| | **Raters:** Not stated to be independent of treatment |
| | **Design:** Multi-centre - 40 centres in the US |
| | **Number of people screened, excluded & reasons:** Not mentioned |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 100% schizophrenia or schizoaffective |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:**<br>- Aged 18 to 60<br>- Met DSM-IV criteria for schizophrenia or schizoaffective disorder<br>- Had prominent depressive symptoms as defined by a score >=16 (mild depression) MADRS and a score >=4 (pervasive feelings of sadness or gloominess) on item 2 (reported sadness) of the MADRS. |

**Exclusion criteria:**
- History of non-response to at least 6 weeks of olanzapine or ziprasidone
- Had received a depot neuroleptic within 2 weeks of visit 1.

**Total sample size:** No. randomised 394

**Total sample size:** ITT population 326

**Total sample size:** Safety population 394

**Gender:** Not stated

**Age:** Mean No mention

**Ethnicity:** Not mentioned

**Setting:** Other Most (99%) were outpatients

**Setting:** Outpatient

**Setting:** Inpatient

**History:** No mention

**Baseline stats:**
[Olanzapine / Ziprasidone]
MADRS: 27.3 (6.2) / 27.3 (6.5)
PANSS: 79.6 (17.5) / 79.1 (17.3)
GAF: 45.6 (10.6) / 46.0 (9.5)

**Notes about participants:** No. participants randomised to each dose unclear

**Interventions**

**Intervention - group 1.:** Olanzapine 10, 15 or 20mg/day; n=202

**Intervention - group 2.:** Ziprasidone, 80, 120 or 160mg/day; n=192

**Notes about the interventions:**
The assigned dosages and titration schedules were within the package insert. The 80-mg/d ziprasidone dose group was dosed at 40mg/d for 3 days then increased to the assigned fixed dosage. The 120-mg/d ziprasidone dose group was dosed at 40 mg/d for 3 days, 80 mg/d for 6 days then increased to the assigned fixed dosage. The 160-mg/d ziprasidone dose group was dosed at 40 mg/d for 3 days, 80 mg/d for 6 days, 120 mg/d for at most 5 days, then increased to the assigned fixed dosage.

Olanzapine was initiated at 10mg/d, and the dosage for the 15- and 20-mg/d dose groups were increased to 15mg/d after 1 week. The 20-mg/d dose group was increased to the assigned fixed dosage by the end of week 2.

During this same 2-week titration period, patients were titrated off previous antipsychotic medication with a requirement set at 50% of their original dosage of prestudy antipsychotic medication by the end of 1 week.

| | |
|---|---|
| | Concomitant medications with psychotropic activity were not allowed, with the following exceptions: benzodiazepines, hypnotics, medication for treatment of extrapyramidal symptoms (EPS) (excluding prophylaxis), and antidepressants if taken in stable doses for at least 30 days before enrolment and maintained throughout the study. |
| **Outcomes** | **Leaving the study early:** Leaving because of adverse effects |
| | **Leaving the study early:** Leaving due to any reason (non-adherence to study protocol) |
| | **Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - CDSS, MADRS, PANSS |
| | **General and psychosocial functioning (e.g. SFS):** Average score/change in general functioning - GAF |
| | **Adverse events:** Number of people with specific adverse effects- Various |
| | **Adverse events:** Average score/change in specific adverse effects- SAS, AIMS, BAS<br>Laboratory values inc. glucose, QTc, vital signs |
| **Quality** | **1.1 The study addresses an appropriate and clearly focused question.:** Well covered |
| | **1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately |
| | **1.3 An adequate concealment method is used.:** Not addressed |
| | **1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered |
| | **1.5 The treatment and control groups are similar at the start of the trial.:** Adequately addressed |
| | **1.6 The only difference between groups is the treatment under investigation.:** Not reported adequately |
| | **1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Adequately addressed |
| | **1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** >50% |
| | **1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Adequately addressed |
| | **1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not reported adequately |
| | **2.1 How well was the study done to minimise bias?: +** |

| | |
|---|---|
| **Study ID** | **LIBERMAN2002** |
| **General info** | **Funding source:** Not mentioned |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |

**Type of analysis:** Completer - No mention of ITT

**Blindness:** Double-blind

**Duration:** No. weeks of treatment 8

**Raters:** Not stated to be independent of treatment

**Design:** Single-centre – Los Angeles, US

**Number of people screened, excluded & reasons:** No mention

**Notes about study methods:** Randomisation procedures not reported

**Participants**

**Diagnosis:** Schizophrenia [% of sample] 100%

**Diagnostic tool:** Other DSM

**Inclusion criteria:**
- DSM-III-R schizophrenia
- Met criteria for treatment refractory illness as defined by Kane et al (13)
- Had at least three 6-week periods of treatment with neuroleptics of at least two different classes at chlorpromazine equivalent of >=1000mg/day in the past 5 years, resulting in either no significant symptom improvement or an intolerance to such doses.

**Exclusion criteria:**
- Any clinically significant neurological disorder
- History of serious head injury
- Physical, cognitive or language impairment sufficient to question the validity of clinical scores
- Substance misuse in past 6 months
- Medication history that included a risperidone trial of sufficient length to determine clinical response
- Treatment with study medications or clozapine within past 4 weeks, or depots within past 8 weeks
- Behaviour that poses significant danger to self or others
- Significant clinical improvement (BPRS <=35) between screening and study entry.

**Total sample size:** No. randomised 36

**Gender:** % female 33%

**Age:** Mean 37.4 (7.5)

**Ethnicity:** No mention

**Setting:** Inpatient

**History:** Age of onset: 17.8 (4.0)

**Baseline stats:** BPRS: 68.2 (14.4)
ADLs: 6.74 (1.0)

| | |
|---|---|
| | **Notes about participants:** 3-week stabilisation phase on haloperidol 15-30mg prior to randomisation. |
| **Interventions** | **Intervention - group 1.:** Risperidone, 6-8mg, n=18 |
| | **Intervention - group 2.:** Haloperidol, 15-20mg, n=18 |
| | **Notes about the interventions:**<br>Study medications were delivered in 4-week fixed dose phase (6mg risperidone or 15mg haloperidol) followed by 4-week flexible dose phase.<br>All participants received highly structured training of activities of daily living (ADL), which included a token economy with points awarded for participation and improvement. |
| **Outcomes** | **General and psychosocial functioning (e.g. SFS):** Average score/change in general functioning - ADL |
| | **Cognitive functioning:** Average score/change in cognitive functioning - WCST, ds-CPT, CVLT, DSDT |
| **Quality** | **1.1 The study addresses an appropriate and clearly focused question.:** Well covered |
| | **1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately |
| | **1.3 An adequate concealment method is used.:** Not addressed |
| | **1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered |
| | **1.5 The treatment and control groups are similar at the start of the trial.:** Adequately addressed |
| | **1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed |
| | **1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Poorly addressed |
| | **1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** <20% |
| | **1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Not addressed |
| | **1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not applicable |
| | **2.1 How well was the study done to minimise bias?: +** |

| | |
|---|---|
| **Study ID** | **MELTZER2008** |
| | **Funding source:** Pharmaceutical industry |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** ITT - Mixed model provided estimates of missing data by using available data from all subjects to estimate the missing |

data

**Blindness:** Double-blind

**Duration:** No. weeks of treatment 36

**Raters:** Not stated to be independent of treatment

**Design:** Multi-centre 3 outpatient CMHTs, US

**Number of people screened, excluded & reasons:** Not reported

**Notes about study methods:** Randomisation used a previously generated randomisation list for each site. No further details reported.

**Participants**

**Diagnosis:** Schizophrenia [% of sample] 82%

**Diagnosis:** Other schizophrenia related [%] Schizoaffective disorder - 18%

**Diagnostic tool:** DSM-IV

**Inclusion criteria:**
- Moderate to severe levels (Score >=4) for at least 2 of the following positive symptoms: delusions, hallucinations, conceptual disorganisation and unusual thought content, despite 2 or more trials of SGA or FGA from different chemical classes, with adequate doses for at least 6 weeks

**Exclusion criteria:**
- History of unresponsiveness to conventional trials at adequate dose of either clozapine or olanzapine
- History of neurological disorder, cardiac disease
- Active substance misuse

**Total sample size:** No. randomised 40

**Total sample size:** ITT population 40

**Gender:** % female 33

**Age:** Mean 37

**Ethnicity:**
[Clozapine / Olanzapine]
Race, N(%):
White: 12(57.1) / 14(73.7)
African American: 8(38.1) / 3(15.8)
Asian: 0(0.0) / 2(12.5)
Other: 1(4.8) / 0(0.0)

**Setting:** Outpatient

**History:**
[Clozapine / olanzapine]
Age at onset: 22.5(7.3) / 19.4(10.5)
Duration of illness, years: 14.7(7.8) / 16.6(12.7)
No of previous hospitalisations: 5.9(4.0) / 6.8(7.8)

**Baseline stats:**
[Clozapine / olanzapine]
PANSS: 91.9(SE 2.3) /92.2(SE 2.4)

**Interventions**

**Intervention - group 1.:** Clozapine, 300-900mg/day, n = 21

**Intervention - group 2.:** Olanzapine, 25-45mg/day, n = 19

**Notes about the interventions:**
Clozapine
Initiated at a dose of 25mg/day for 2 days, > 25-50mg/day for days 3 and 4, increased further by 25mg increments until a target dose of 400mg/day was reached on days 17 and 18. Dose could then be increased to a max of 900mg/day based upon response and tolerability

Olanzapine
Initiated at 10mg/day for 1 week, after which dose increased to 15mg/day on days 8-14 and 20mg/day on 15-18. Dose could then be increased to a maximum of 45mg/day
Haloperidol was permitted as a rescue medication.
During the maintenance phase 9 capsules, each of which contained 100mg clozapine, olanzapine 5mg or placebo.

**Outcomes**

**Leaving the study early:** Leaving because of adverse effects

**Global state & service outcomes (e.g. CGI):** Average score/change in global state - GAF

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS; SANS; SAPS

**Adverse events:** Average score/change in specific adverse effects - AIMS; SAS

**Cognitive functioning:** Average score/change in cognitive functioning Cognitive functioning

**Other:** BMI; Weight

**Quality**

**1.1 The study addresses an appropriate and clearly focused question.:** Well covered

**1.2 The assignment of subjects to treatment groups is randomised.:** Adequately addressed

**1.3 An adequate concealment method is used.:** Not addressed

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered

**1.5 The treatment and control groups are similar at the start of the trial.:** Well covered

**1.6 The only difference between groups is the treatment under investigation.:** Well covered

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** 20-50%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Well covered

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not addressed

**2.1 How well was the study done to minimise bias?:** +

| **Study ID** | **SEE1999** |
|---|---|
| **General info** | **Funding source:** Pharmaceutical industry |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** Completer |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment - 5 |
| | **Raters:** Not stated to be independent of treatment |
| | **Design:** Single-centre - Kuwait |
| | **Number of people screened, excluded & reasons:** Not reported |
| | **Notes about study methods:** Randomisation procedure not reported |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 100% |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:**<br>- Aged 18+<br>- Primary diagnosis of schizophrenia<br>- History of partial responsiveness to typical antipsychotic with residual symptoms. |
| | **Exclusion criteria:** Not reported |
| | **Total sample size:** No. randomised 20 |
| | **Gender:** % female 30% |

**Age:** Mean 35

**Ethnicity:** Not reported

**Setting:** Inpatient

**History:** Mean duration of illness = ~10 years

**Baseline stats:**
[Risperidone / Haloperidol]
PANSS total: 76.50 (4.23) / 79.25 (4.67)

**Interventions**

**Intervention - group 1.:** Risperidone, 4–6 mg/day, n =10

**Intervention - group 2.:** Haloperidol, 15–30 mg/day, n = 10

**Notes about the interventions:**
- All participants were given a 3-week open-label trial of trifluoperazine (20–30 mg/day)
- During the week 1, trifluoperazine dose was reduced to between 5 and 10 mg/day, and daily doses of haloperidol increased to 15-30 mg/day and risperidone were to 4–6 mg/day.
-During week 2, all trifluoperazine was discontinued.
- Antiparkinsonism medication was available as needed

**Outcomes**

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS, PANSS negative, PANSS positive

**Adverse events:** Average score/change in specific adverse effects- SAS

**Other:** NE levels as measured by blood samples

**Quality**

**1.1 The study addresses an appropriate and clearly focused question.:** Adequately addressed

**1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately

**1.3 An adequate concealment method is used.:** Not addressed

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered

**1.5 The treatment and control groups are similar at the start of the trial.:** Not reported adequately

**1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Adequately addressed

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** <20%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis).**
**:** Poorly addressed

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not applicable

**2.1 How well was the study done to minimise bias?:** +

| Study ID | VOLAVKA2002 |
|---|---|
| General info | **Funding source:** Pharmaceutical industry |
| | **Published or unpublished data?:** Published |
| Method | **Type of study:** Individual randomised trial |
| | **Type of analysis:** LOCF |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment - 14 |
| | **Raters:** Not stated to be independent of treatment |
| | **Design:** Multi-centre - 4 psychiatric hospitals in New York, US |
| | **Number of people screened, excluded & reasons:** 167 randomised, 10 dropped out before starting medication |
| | **Notes about study methods:** The study originally had three arms in June 1996, and the olanzapine arm was added at a later stage (in November 1997), which required a modified randomisation procedure. This entails the potential for a bias that could be manifested as a cohort effect. However, blind conditions were never compromised since all tablets looked alike, and subjects continued to be assigned to the original three treatments at rates that were unknown to the study personnel and subjects. |
| Participants | **Diagnosis:** Schizophrenia [% of sample] 86% |
| | **Diagnosis:** Other schizophrenia related [%] Schizoaffective 14% |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:**<br>- Aged 18-60<br>- DSM-IV diagnosis of schizophrenia or schizoaffective disorder<br>- Sub-optimal response to previous treatment, defined by history of persistent positive symptoms after at least 6 contiguous weeks of treatment with one or more typical antipsychotics at >=600mg/day in chlorpromazine equivalents; and a poor level of functioning over past 2 years, defined by the lack of competitive employment or enrolment in an academic or vocational programme and not having age-expected interpersonal relations with someone outside the biological family of origin with who ongoing regular contacts are maintained<br>- PANSS >=60 |
| | **Exclusion criteria:**<br>- History of non-response to clozapine, risperidone or olanzapine, defined as an unambiguous lack of improvement despite a contiguous adequate trial of risperidone or olanzapine for >=6 weeks, or clozapine for >=14 weeks<br>- History of clozapine, olanzapine, risperidone or haloperidol intolerance |

- Received a depot antipsychotic in the past 30 days.

**Total sample size:** ITT population 157

**Total sample size:** No. randomised 167

**Gender:** % female 15%

**Age:** Mean 40.8 (9.2)

**Setting:** Inpatient

**History:**
Years of illness: 19.5 (8.4)
Hospitalisations: 10.5 (8.3)

**Baseline stats:**
PANSS
Clozapine: 97.6 (17.1)
Olanzapine: 91.0 (13.5)
Risperidone: 89.5 (13.8)
Haloperidol: 90.4 (11.6)

**Notes about participants:** During 1-2 week baseline period, prestudy medication so that daily dose <=750mg/day chlorpromazine equivalent. Concomitant medications such as mood stabilisers and antidepressants were gradually tapered and discontinued.

**Interventions**

**Intervention - group 1.:** Clozapine, 200-800mg, n=40

**Intervention - group 2.:** Olanzapine, 10-40mg/day, n=39

**Intervention - group 3.:** Risperidone 4-16mg/day, n=41

**Intervention - group 4.:** Haloperidol 10-30mg/day, n=37

**Notes about the interventions:**
Study medication doses were titrated to maximise efficacy and minimise side effects. All patients received benztropine, benztropine placebo or both. Haloperidol group received 4mg/day prophylactically. All patients could be prescribed benztropine (up to 6mg/day) if judged to require treatment for EPS. Propranolol was allowed for treatment of akathisia. Lorazepam, diphenhydramine hydrochloride or chloral hydrate were prescribed open-label as needed for agitation or insomnia. No other adjunctive psychotropic medications were allowed.

**Outcomes**

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Leaving the study early:** Leaving because of adverse effects

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS

**Adverse events:** Number of people with specific adverse effects - Severe blood disorders, seizures, hypertensive episodes

**Adverse events:** Average score/change in specific adverse effects - EPS Rating Scale, weight gain

**Quality**

**1.1 The study addresses an appropriate and clearly focused question.:** Well covered

**1.2 The assignment of subjects to treatment groups is randomised.:** Poorly addressed

**1.3 An adequate concealment method is used.:** Not addressed

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered

**1.5 The treatment and control groups are similar at the start of the trial.:** Well covered

**1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** 20-50%

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not reported adequately

**2.1 How well was the study done to minimise bias?:** +

**References of included studies (update)**

**BUCHANAN2005**

Buchanan,R.W.; Ball,M.P.; Weiner,E.; Kirkpatrick,B.; Gold,J.M.; McMahon,R.P.; Carpenter,W.T. (2005) Olanzapine treatment of residual positive and negative symptoms. *The American Journal of Psychiatry.* 162: 124 - 129.

**CONLEY2005**

Conley,R.R.; Kelly,D.L.; Nelson,M.W.; Richardson,C.M.; Feldman,S.; Benham,R.; Steiner,P.; Yu,Y.; Khan,I.; McMullen,R.; Gale,E.; Mackowick,M.; Love,R.C. (2005) Risperidone, quetiapine, and fluphenazine in the treatment of patients with therapy-refractory schizophrenia. *Clinical Neuropharmacology.* 28: 163 - 168.

Kelly,D.L.; Conley,R.R. (2006) A randomized double-blind 12-week study of quetiapine, risperidone or fluphenazine on sexual functioning in people with schizophrenia. *Psychoneuroendocrinology.* 31(**3**): 340 - 346.

**KANE2007B**

Kane,J.M.; Meltzer,H.Y.; Carson,W.H.; McQuade,R.D.; Marcus,R.N.; Sanchez,R.; Aripiprazole-Study-Group (2007) Aripiprazole for treatment-resistant schizophrenia: results of a multicenter, randomized, double-blind, comparison study versus perphenazine. *The Journal of Clinical Psychiatry* 68: 213 - 223.

**KINON2006A**

Kinon,B.J.; Lipkovich,I.; Edwards,S.B.; Adams,D.H.; scher-Svanum,H.; Siris,S.G. (2006) A 24-week randomized study of olanzapine versus ziprasidone in the treatment of schizophrenia or schizoaffective disorder in patients with prominent depressive symptoms. *Journal of Clinical Psychopharmacology.* 26(**2**).

**LIBERMAN2002**

Liberman,R.P.; Gutkind,D.; Mintz,J.; Green,M.; Marshall,B.D.,Jr.; Robertson,M.J.; Hayden,J. (2002) Impact of risperidone versus haloperidol on activities of daily living in the treatment of refractory schizophrenia. *Comprehensive Psychiatry.* 43(**6**): 469 - 473.

**MELTZER2008**

Meltzer,H.Y.; Bobo,W.V.; Roy,A.; Jayathilake,K.; Chen,Y.; Ertugrul,A.; Anil Yagcioglu, AE; Small,J.G. (2008) A randomized, double-blind comparison of clozapine and high-dose olanzapine in treatment-resistant patients with schizophrenia. *Journal of Clinical Psychiatry.* 69(**2**): 274 - 285.

**SEE1999**

See RE, Fido AA, Maurice M, Ibrahim MM, Salama GM. (1999) Risperidone-induced increase of plasma norepinephrine is not correlated with symptom improvement in chronic schizophrenia. *Biological Psychiatry* 45(**12**): 1653-6.

**VOLAVKA2002**

Bilder,R.M.; Goldman,R.S.; Volavka,J.; Czobor,P.; Hoptman,M.; Sheitman,B.; Lindenmayer,J.P.; Citrome,L.; McEvoy,J.; Kunz,M.; Chakos,M.; Cooper,T.B.; Horowitz,T.L.; Lieberman,J.A. (2002) Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. *American Journal of Psychiatry.* 159(**6**): 1018 - 1028.

Czobor,P.; Volavka,J.; Sheitman,B.; Lindenmayer,J.P.; Citrome,L.; McEvoy,J.; Cooper,T.B.; Chakos,M.; Lieberman,J.A. (2002) Antipsychotic-induced weight gain and therapeutic response: a differential association. *Journal of Clinical Psychopharmacology.* 22(**3**): 244 - 251.

Lindenmayer,J.P.; Czobor,P.; Volavka,J.; Citrome,L.; Sheitman,B.; McEvoy,J.P.; Cooper,T.B.; Chakos,M.; Lieberman,J.A. (2003) Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical or atypical antipsychotics. *American Journal of Psychiatry.* 160(**2**): 290 - 296.

Volavka,J.; Czobor,P.; Cooper,T.B.; Sheitman,B.; Lindenmayer,J.P.; Citrome,L.; McEvoy,J.P.; Lieberman,J.A. (2004) Prolactin levels in schizophrenia and schizoaffective disorder patients treated with clozapine, olanzapine, risperidone, or haloperidol. *The Journal of Clinical Psychiatry.* 65: 57 - 61.

Volavka,J.; Czobor,P.; Nolan,K.; Sheitman,B.; Lindenmayer,J.P.; Citrome,L.; McEvoy,J.P.; Cooper,T.B.; Lieberman,J.A. (2004) Overt aggression and psychotic symptoms in patients with schizophrenia treated with clozapine, olanzapine, risperidone, or haloperidol. *Journal of Clinical Psychopharmacology*. 24: 225 - 228.

*Volavka,J.; Czobor,P.; Sheitman,B.; Lindenmayer,J.P.; Citrome,L.; McEvoy,J.P.; Cooper,T.B.; Chakos,M.; Lieberman,J.A. (2002) Clozapine, olanzapine, risperidone, and haloperidol in the treatment of patients with chronic schizophrenia and schizoaffective disorder. [erratum appears in *American Journal of Psychiatry* 2002 Dec;159(12):2132]. *American Journal of Psychiatry*. 159(**2**): 255 - 262.

**Characteristics of excluded studies (previous guideline)**

| Study | Reason for exclusion |
|---|---|
| **Chiu 1976** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant) |
| **Chow 2000** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant) |
| **Ciurezu 1976** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant) |
| **Cosar 1999** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant) |
| **Covington 2000** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant) |
| **Essock 1996** | Interventions: Clozapine vs. usual care<br>Blinding: not double-blind |
| **Erlandsen 1981** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant) |
| **Fisher-Cornelssen 1974** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant) |
| **Fisher-Cornelssen 1976a** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant) |
| **Fisher-Cornelssen 1976b** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant) |
| **Fleming 1998** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant) |

| | |
|---|---|
| **Gerlach 1974** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant) |
| **Gerlach 1975** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant) |
| **Guirguis 1977** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant) |
| **Honifeld 1984** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant) |
| **Howanitz 1999** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant) |
| **Itoh 1977** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant) |
| **Klieser 1994** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant) |
| **Kumra 1996b** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant) |
| **Lee 1994c** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant) |
| **Leon 1974** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant) |
| **Salganik 1998** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant) |
| **Shopsin 1979a** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant) |
| **Singer 1974** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant) |
| **Tamminga 1994d** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant) |
| **Xu 1985** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant) |
| **Xu 1989** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant) |

| | |
|---|---|
| **Xu 1994** | Allocation: randomised<br>Participants: people with schizophrenia (not treatment-resistant) |

**References of excluded studies (previous guideline)**

**Chiu 1976**

Chiu E, Burrows G, Stevenson J. (1976) Double-blind comparison of clozapine with chlorpromazine in acute schizophrenic illness. *Australian and New Zealand Journal of Psychiatry*; 10(4):343-347.

**Chow 2000**

Chow E, Desai H, Selhi Z, Bassett AS, Collins E. (2000) A study to evaluate the antiaggressive properties of clozapine. *Schizophrenia Research*; 41(1):183.

**Ciurezu 1976**

Ciurezu T, Ionescu R, Nica Udangiu S, Niturad D, Oproiu L, Tudorache D, et al 1976). Etude clinique en 'double blind' du HF 1854 (LX 100-129, clozapine ou leponex) compare a l'haloperidol. [Double-blind clinical study of HF 1854 (LX 100-129, clozapine or leponex) as compared with haloperidol]. *Neurologie et Psychiatrie ( Bucur*); 14(1):29-34.

**Cosar 1999**

Cosar B, Candansayar S, Taner E, Isik E. (1999) Comparison of efficacy of clozapine, sulpiride, chlorpromazine and haloperidol in chronic schizophrenic patients therapy. *European Neuropsychopharmacology*; 9(suppl. 5):S287.

**Covington 2000**

Covington L, Cola PA. (2000) Clozapine vs. haloperidol: Antipsychotic effects on sexual function in schizophrenia. *Sexuality and Disability*; 18(1):41-48.

**Erlandsen 1981**

Erlandsen C. (1981) Trial of a new neuroleptic drug, Leponex (clozapine) in long-standing schizophrenia. *Nordisk Psykiatrisk Tidsskrift*; 35(3):248-253.

**Essock 1996**

Essock SM, Hargreaves WA, Covell NH, Goethe J. (1996) Clozapine's effectiveness for patients in state hospitals: results from a randomized trial. *Psychopharmacology Bulletin*; 32:683-97.

**Fisher-Cornelssen 1974**

Fischer-Cornelssen K, Ferner U, Steiner H. (1974) Multifokale Psychopharmakaprufung ("Multihospital trial"). *Arzneimittelforschung*; 24:1706-24.

**Fisher-Cornelssen 1976a/b**

Fischer-Cornelssen KA, Ferner UJ. (1976) An example of European multicenter trials: multispectral analysis of clozapine. *Psychopharmacology Bulletin*; 12:34-9.

**Fleming 1998**

Fleming K, Potkin SG, Alva G, Carreon D. (1999) Dissociation of improvement in neurocognition and negative symptomatology with olanzapine and clozapine. *Schizophrenia Research*; 36(1-3):279.

**Gelenberg 1979**

Gelenberg AJ, Doller JC. (1979) Clozapine versus chlorpromazine for the treatment of schizophrenia: preliminary results from a double-blind study. *Journal of Clinical Psychiatry*; 40:238-240.

**Gerlach 1974**

Gerlach J, Koppelhus P, Helweg E, Monrad A. (1974) Clozapine and haloperidol in a single-blind cross-over trial: therapeutic and biochemical aspects in the treatment of schizophrenia. *Acta Psychiatrica Scandinavica*; 50:410-24.

**Gerlach 1975**

Gerlach J, Thorsen K, Fog R. (1975) Extrapyramidal reactions and amine metabolites in cerebrospinal fluid during haloperidol and clozapine treatment of schizophrenic patients. *Psychopharmacologia*; 40:341-350.

**Guirguis 1977**

Guirguis E, Voineskos G, Gray J, Schlieman E. (1977) Clozapine (leponex) vs Chlorpromazine (Largactil) in acute schizophrenia (a double-blind controlled study). *Current Therapeutic Research, Clinical and Experimental*; 21(5):707-719.

**Honigfeld 1984**

Honigfeld G, Patin J, Singer J. (1984) Clozapine: antipsychotic activity in treatment resistant schizophrenics. *Advances in Therapy*; 1(2):77-97.

**Howanitz 1999**

Howanitz E, Pardo M, Smelson DA, Engelhart C, Eisenstein N, Losonczy ME. (1999) The efficacy and safety of clozapine versus chlorpromazine in geriatric schizophrenia. *Journal of Clinical Psychiatry*; 60(1):41-44.

**Itoh 1977**

Itoh H, Miura S, Yagi G, Sakurai S, Ohtsuka N. (1977) Some methodological considerations for the clinical evaluation of neuroleptics--comparative effects of clozapine and haloperidol on schizophrenics. *Folia Psychiatrica et Neurologica Japonica*; 31(1):17-24.

**Klieser 1994**

Klieser E, Strauss WH, Lemmer W. (1994) The tolerability and efficacy of the atypical neuroleptic remoxipride compared with clozapine and haloperidol in acute schizophrenia. *Acta Psychiatrica Scandinavica*; 89(suppl 380):68-73.

**Kumra 1996**

Kumra S, Frazier JA, Jacobsen LK, McKenna K, Gordon CT, Lenane MC, et al. (1996) Childhood-onset schizophrenia. A double-blind clozapine-haloperidol comparison. *Archives of General Psychiatry*; 53(12):1090-7.

**Lee 1994**

Lee M, Thompson P, Meltzer H. (1994) Effects of clozapine on cognitive function in schizophrenia. *Journal of Clinical Psychiatry*; 55(sB):82-87.

**Leon 1974**

Leon CA, Estrada H. (1974) Therapeutic effect of clozapine on psychotic symptoms (clinical evaluation using the double-blind method). *Revista Columbiana de Psiquiatria*; 3:309-320.

**Salganik 1998**

Salganik I, Modai I, Bercovici BR, Kutzuk D, Weizman A. (1998) Clozapine vs haloperidol therapy in elderly chronic schizophrenic inpatients - Preliminary results. A double-blind, cross-over randomized study. *International Journal of Geriatric Psychopharmacology*; 1(4):185-187.

**Shopsin 1979**

Shopsin B, Klein H, Aaronsom M, Collora M. (1979) Clozapine, chlorpromazine, and placebo in newly hospitalized, acutely schizophrenic patients: a controlled, double-blind comparison. *Archives of General Psychiatry*; 36:657-64.

**Singer 1974**

Singer K, Law S. (1974) Comparative double-blind study with clozapine (Leponex) and chlorpromazine in acute schizophrenia. *Journal of International Medical Research*; 2:433-5.

**Tamminga 1994**

Tamminga CA, Thaker GK, Moran M, Kakigi T, Gao XM. (1994) Clozapine in tardive dyskinesia: observations from human and animal model studies. *Journal of Clinical Psychiatry*; 55(suppl B):102-6.

**Wahlbeck 2000**

Wahlbeck K, Cheine M, Tuisku K, Ahokas A, Joffe G, Rimon R. (2000) Risperidone versus clozapine in treatment-resistant schizophrenia: a randomised pilot study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*; 24(6):911-922.

**Xu 1985**

Xu WR, Bao-long Z, Qui C, Mei-Fang G. (1985) A double-blind study of clozapine and chlorpromazine treatment in the schizophrenics. *Chinese Journal of Nervous and Mental Diseases*; 11(4):222-224.

**Xu 1989**

Potter WZ, Ko GN, Zhang L-D, Yan W. (1989) Clozapine in China: A review and preview of US/PRC collaboration. *Psychopharmacology*; 99(suppl):87-91.

**Xu 1994**

Liu B, Chen Y, Yang D. (1994) Effects of thioridazine on schizophrenics and clinical utility of plasma levels. *Chinese Journal of Neurology and Psychiatry* ;27(6):364-367.

# Promoting recovery in people with schizophrenia whose illness has not responded adequately to treatment (persistent negative symptoms)

**Characteristics of included studies (previous guideline)**

| Study | Methods | Participants | Interventions | Outcomes | Notes |
|---|---|---|---|---|---|
| **Boyer 1990** | Allocation:<br>Random – no further details.<br><br>Blinding:<br>Not described.<br><br>Duration:<br>6 weeks, preceded by a 3 week washout period.<br><br>Setting:<br>Probably a single centre. Not clear whether in-patients or out-patients. | Diagnosis:<br>Schizophrenia (DSM-III), disorganised, catatonic or residual types.<br><br>Age: 21-53<br><br>Sex: 43 M, 19 F<br><br>N: 62<br><br>History:<br>Not stated (chronic?)<br>All met Andreasen criteria for negative symptoms.<br>Absence of marked positive symptoms. Score >7 on Defective Symptoms Assessment Scale (DSAS).<br>Duration of illness 1-20 years (mean 9.2 years (amisulpride) and 12.3 years (fluphenazine)).<br>Mean number of previous hospitalisations 2.9 (amisulpride), 4.4 (fluphenazine). | 1. amisulpride: dose 50-300mg/day (flexible dose), mean = 225 mg/day. n = 34.<br><br>2. fluphenazine: dose 2-12mg/day (flexible dose), mean = 10 mg/day. n = 28. | Leaving the study early.<br><br>Mental state:<br>BPRS global, anxiety/depression and anergia subscores;<br>NOSIE<br>CHESS (Clinical Hepatic Encephalopathy Staging Scale)<br><br>Unable to use:<br>Mental state:<br>DSAS score (not validated). | No details on dropout or ITT analysis were given. |

| | | | | | |
|---|---|---|---|---|---|
| **Lecrubier 1999** | Allocation: randomised, computer-generated, blocks for each investigator, 2:2:2:1, concealed from investigator.<br>Blindness: double, medication kits issued.<br>Duration: 6 months. | Diagnosis: "schizophrenic patients with primarily negative symptoms" (DSM-IV)<br>Inclusion criteria: minimum SANS summary score of 10 (excluding attention subscore) and no score > 4 on hallucination & delusion items of PANSS (normalised, scored 0-6).<br>N=245.<br>Age: mean 37.6 years.<br>Sex: 32% F.<br>Setting: Inpatient or outpatient | 1. Olanzapine: dose 5mg/day. n=70.<br>2. Olanzapine: dose 20mg/day. n=70.<br>3. Placebo: n=35<br>4. Amisulpride: dose 150mg/day. n=70. | Leaving study early.<br>Mental state: SANS.<br>Other adverse events: COSTART list, weight change.<br>Quality of life: Carpenter QLS.<br><br>Unable to use -<br>Mental state: PANSS (no useable data).<br>Side effects: extrapyramidal (no data). | |
| **Murasaki 1999 (Japan 1999b)** | Allocation: randomised, no further details.<br>Blindness: double blind, no further details.<br>Duration: 8 weeks (no details of washout period) | Diagnosis: schizophrenia (DSM-IV or ICD-10)<br>Inclusion criteria: no details<br>N=197<br>Age: mean 45 years<br>Sex: M 129, F 68 | Quetiapine: mean dose 226mg/day. n=100.<br>Haloperidol: mean dose 6.7mg/day. n=97. | Mental state – general: BPRS, PANSS.<br>Mental state – specific: PANSS-P, PANSS-N.<br>Side-effects: extrapyramidal – the number of participants reporting EPS-related events.<br>Leaving the study early | |

| | | | | | |
|---|---|---|---|---|---|
| **Speller 1997** | Allocation:<br>Random – no further details.<br><br>Blinding:<br>Double – no further details.<br><br>Duration:<br>1 year, preceded by a 3 month washout period for those previously on depot medication (during which they received an equivalent dose of oral haloperidol), otherwise no washout period.<br><br>Setting:<br>Multicentre. 18 continuing care and rehabilitation wards at two psychiatric hospitals. Inpatients. | Diagnosis:<br>Schizophrenia (DSM-III-R).<br><br>Age: 35-76<br><br>Sex: 46M, 14F<br><br>N: 60<br><br>History:<br>Chronic, with moderate to severe negative symptoms. Combined score of >=4 on flatness of affect and poverty of speech items on the Manchester scale. Excluded if taking antipsychotic drug dose equivalent to 1200mg a day or more of chlorpromazine. Duration of illness 109 – 660 months (mean 432 – 452 months). | 1. amisulpride: initial dose either 800mg, 600mg, 450mg, 300mg, 150mg or 100mg*. Dose reduced every 3 months, where possible, according to severity of symptoms. n = 29.<br><br>2. haloperidol: dose 20mg, 16mg, 11.5mg, 8mg, 5mg, 3mg*. Dose reduced every 3 months, where possible, according to severity of symptoms. n = 31.<br><br>*initial dose levels calculated to be closest equivalent to previous antipsychotic medication. Systematic dose reduction over the course of the trial, as symptoms allowed. | Leaving the study early<br><br>Global state:<br>Psychotic exacerbations. Achieved or maintained low dose level at endpoint.<br><br>Mental state:<br>MS negative subscale (response and change)<br>SANS items<br>BPRS negative subscale<br>MS positive subscale<br><br>Side effects<br>BARS<br><br>Unable to use:<br>SBS (social behaviour scale – no data) | Efficacy analysis carried out on the 54 participants remaining in the study after 3 months. |

**References of included studies (previous guideline)**

**Boyer 1990**

Boyer P, Lecrubier Y, Puech AJ. (1990) Treatment of positive and negative symptoms: Pharmacologic approaches. In: Andreasen NC, ed. *Schizophrenia: Positive and Negative Symptoms and Syndromes*, pp. 152-174. Basel, Switzerland: S. Karger AG.

**Lecrubier 1999**

*Lecrubier Y, Bouhassira M, Olivier V, Lancrenon S, Crawford AM. (1999) Olanzapine versus amisulpride and placebo in the treatment of negative symptoms and deficit states of chronic schizophrenia. *European Neuropsychopharmacology*; 9(suppl 5):S288.

Lecrubier,Y.; Quintin,P.; Bouhassira,M.; Perrin,E.; Lancrenon,S. (2006) The treatment of negative symptoms and deficit states of chronic schizophrenia: olanzapine compared to amisulpride and placebo in a 6-month double-blind controlled clinical trial. *Acta Psychiatrica Scandinavica*. 114(5): 319 - 327.

**Murasaki 1999 (Japan 1999b)**

Murasaki M, Koyama T, Yamauchi T, Yagi MG, Ushijima S, Kamijima K. (1999) Clinical evaluation of quetiapine in schizophrenia - efficacy and tolerability of quetiapine compared with haloperidol in patients with schizophrenia. In: *Annual Meeting of the World Psychiatric Association*; August 6-11 1999; Hamburg, Germany.

**Speller 1997**

Speller JC, Barnes TRE, Curson DA, Pantelis C, Alberts JL. (1997) One-year, low-dose neuroleptic study of in-patients with chronic schizophrenia characterised by persistent negative symptoms: Amisulpride v. haloperidol. *British Journal of Psychiatry*; 171:564-568.

**Characteristics of included studies (update)**

| **Study ID** | **HERTLING2003** |
|---|---|
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of study:** Individual randomised trial (Noninferiority/equivalence) |
| | **Type of analysis:** ITT - Completed at least 8 weeks of treatment (for primary analyses) |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment 25 |
| | **Raters:** Not stated to be independent of treatment |
| | **Design:** Multi-centre - 30 centres in Germany and Austria |
| | **Number of people screened, excluded & reasons:** 153 randomised, 144 included in statistical analyses |
| | **Notes about study methods:** Randomisation procedures not reported |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 100% |

| | |
|---|---|
| | **Diagnostic tool:** ICD-10 |
| | **Inclusion criteria:**<br>- Aged 18-65<br>- Met ICD-10 criteria F20.0-20.3, 20.5-20.9 excluding acute psychosis<br>- Duration of illness >=2 years<br>- At least 3 items >=4 points in the PANSS Negative subscale. |
| | **Total sample size:** No. randomised 153 |
| | **Total sample size:** ITT population 144 |
| | **Gender:** % female 38% |
| | **Age:** Mean 40 |
| | **Setting:** Outpatient |
| | **Setting:** Inpatient |
| | **Baseline stats:** No significant differences between groups |
| **Interventions** | **Intervention - group 1.:** Flupenthixol, 4-12mg/day, n=76 |
| | **Intervention - group 2.:** Risperidone, 2-6mg/day, n=77 |
| | **Notes about the interventions:** Dosage was adjusted as indicated. |
| **Outcomes** | **Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS, MADRS |
| | **Adverse events:** Average score/change in specific adverse effects - ESRS |
| | **Satisfaction with treatment:** Service user satisfaction - DAI |
| | **Quality of Life:** Average score/change in quality of life - EuroQoL |
| **Quality** | **1.1 The study addresses an appropriate and clearly focused question.:** Well covered |
| | **1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately |
| | **1.3 An adequate concealment method is used.:** Not addressed |
| | **1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered |
| | **1.5 The treatment and control groups are similar at the start of the trial.:** Adequately addressed |
| | **1.6 The only difference between groups is the treatment under investigation.:** Well covered |
| | **1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered |
| | **1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** 20-50% |
| | **1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** |

Adequately addressed

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not reported adequately

**2.1 How well was the study done to minimise bias?:** +

| **Study ID** | **KINON2006B** |
|---|---|
| **General info** | **Funding source:** Any pharmaceutical industry support |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** ITT - All participants with at least one post-baseline assessment |
| | **Type of analysis:** LOCF |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment - 24 |
| | **Raters:** Not stated to be independent of treatment |
| | **Design:** Multi-centre - US |
| | **Number of people screened, excluded & reasons:** No mention |
| | **Notes about study methods:** Patients were assigned to treatment groups based on a computer-generated randomization code. The randomisation was balanced by using permuted blocks and was stratified by site. All study medication was identical in appearance and was dispensed to subjects by study site personnel. |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 67% |
| | **Diagnosis:** Other schizophrenia related [%] Schizoaffective bipolar 23%<br>Schizoaffective depression 10% |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:**<br>- Met DSM-IV criteria for schizophrenia or schizoaffective disorder<br>- Met criteria for prominent negative symptoms, defined as a PANSS >=4 (moderate) on at least 3, or >=5 (moderately severe) on at least 2 of the 7 negative scale items; and for social and functional impairment, defined as a GAF <=60 (moderate difficulties). |
| | **Total sample size:** No. randomised 346 |
| | **Total sample size:** ITT population - Varied |
| | **Total sample size:** Safety population 346 |

**Gender:** % female 35%

**Age:** Mean 41

**Ethnicity:** White 52%
African descent 37%
Hispanic 9%
Other 2%

**Setting:** Outpatient

**History:**
[Olanzapine / Quetiapine]
Age of psychosis onset: 24.16 (8.73) / 22.59 (7.62)
Years of illness: 17.57 (9.65) / 17.78 (9.39)

**Baseline stats:**
[Olanzapine / Quetiapine]
GAF: 43.24 (8.71) / 43.19 (9.73)
SANS: 61.4 (17.4) / 60.4 (18.4)
PANSS Total: 84.1 (12.8) / 85.2 (14.8)
CGI-S: 4.2 (0.6) / 4.3 (0.7)

**Interventions**

**Intervention - group 1.:** Olanzapine 10-20mg/day, n=171

**Intervention - group 2.:** Quetiapine 300-700mg/day, n=175

**Notes about the interventions:**
Patients' current antipsychotic medications were tapered off as their study medication was initiated. During study period 3, patients were titrated up to their clinically optimal dose of study drug (OLZ, 10–20 mg/d in 5mg increments; QUE, 300–700 mg/d in 100-mg increments). Dosage increases could occur at 7-day intervals after visit 4. Dosage decreases could occur at any time; however, the dose could not decrease below 10 mg/d for OLZ or 300 mg/d for QUE. Patients who required more than 2 dose decreases or dosages less than the minimum allowed were discontinued from the study. Dosing was flexible, and investigators were encouraged to use the highest doses necessary in both treatment groups. All study medication was administered twice daily. Each patient was treated at community mental health centres and assigned case managers, who developed a 6-month treatment plan for illness management and recovery in collaboration with the patient.

**Outcomes**

**Leaving the study early:** Leaving because of adverse effects

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Global state & service outcomes (e.g. CGI):** Average score/change in global state - CGI

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - SANS, PANSS, CDS, CMRS+

**General and psychosocial functioning (e.g. SFS):** Average score/change in general functioning - GAF, PFQ, CMRS+

| | |
|---|---|
| | **Adverse events:** Average score/change in specific adverse effects SAS, BAS, AIMS, use of anticholinergic medication Laboratory tests, weight, BMI |
| | **Adverse events:** Number of people with specific adverse effects Various |
| | **Adverse events:** Number of people with general adverse effects |
| | **Quality of Life:** Average score/change in quality of life QLS |
| **Quality** | **1.1 The study addresses an appropriate and clearly focused question.:** Well covered |
| | **1.2 The assignment of subjects to treatment groups is randomised.:** Well covered |
| | **1.3 An adequate concealment method is used.:** Well covered |
| | **1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered |
| | **1.5 The treatment and control groups are similar at the start of the trial.:** Well covered |
| | **1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed |
| | **1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered |
| | **1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** >50% |
| | **1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Well covered |
| | **1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not reported adequately |
| | **2.1 How well was the study done to minimise bias?:** ++ |

| | |
|---|---|
| **Study ID** | **LINDENMAYER2007** |
| **General info** | **Funding source:** Any pharmaceutical industry support |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** ITT - For all patients who did not complete the entire study, a likelihood-based repeated measures model (mixed models repeated measures) was applied. |
| | **Type of analysis:** LOCF - applied to PANSS data only if patients completed >= 8 weeks of the study |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment 12 |
| | **Raters:** Not stated to be independent of treatment |

**Design:** Single-centre - State psychiatric hospital, New York, US

**Number of people screened, excluded & reasons:** 36 participants were enrolled in the study, 35 were randomly assigned. One patient did not receive study treatment due to withdrawal of consent.

**Notes about study methods:** Randomisation procedure not reported

**Participants**

**Diagnosis:** Schizophrenia [% of sample] 100%

**Diagnostic tool:** DSM-IV

**Inclusion criteria:**
- aged 18-60
- PANSS total score >=50, with a PANSS negative subscale score >=20. The negative symptom score was required to contain >=3 items scores of >=3
- All participants fulfilled the criteria for the Schedule for the Deficit Syndrome (SDS) which included negative symptoms that are stable rather then unstable-state manifestations.

**Exclusion criteria:**
- PANSS depression item score >=4, PANSS positive symptom subscale score of >=20
- SAS score >=2
- History of treatment failure on antipsychotics (persistent positive symptoms after 8 weeks of treatment with adequate doses of 1 or more antipsychotics.)
- Significant medical disorder
- positive substance misuse diagnosis within the last 3 months.
- Pregnant or breastfeeding women and women of childbearing age not using adequate contraception

**Total sample size:** ITT population Unclear

**Total sample size:** No. randomised 35

**Gender:** % female 6%

**Age:** Mean 39

**Ethnicity:** White - 6%
African American - 78%
Hispanic - 13%
Other - 3%

**Setting:** Inpatient

**Setting:** Outpatient

**Baseline stats:**
[Haloperidol / Olanzapine]

PANSS total: 70.79(9.86) / 71.25(17.46)
HAM-D: 5.58(3.13) / 5.74(4.00)

**Notes about participants:**
[Haloperidol / Olanzapine]
Prior antipsychotic treatment, n
Haloperidol: 4 / 2
Thiothixene: 1 / 1
Olanzapine: 2 / 0
Risperidone: 8 / 10
Thioridazine: 1 / 0
Fluphenazine: 2 / 2
Aripiprazole: 1 / 0
Ziprasidone: 1 / 0
Quetiapine: 2 / 1
No previous antipsychotic: 0 / 1

**Interventions**

**Intervention - group 1.:** Haloperidol, 15-20 mg/day; n=19

**Intervention - group 2.:** Olanzapine, 15-20mg/day; n=16

**Notes about the interventions:**
Patients on antipsychotics decanoate preparations prior to the study were converted to oral tablets at equivalent doses at least 3 weeks prior to entry.

- participants started with a fixed dose of olanzapine (15mg/day) or haloperidol (15mg/day) for the first 6 weeks after 1 week of cross-titration from previous medication.
- fixed dose period was followed by a 6-week double-blind, flexible dose phase.
- dose of medication could be increased or decreased by 5mg/day at 2-week intervals during the second phase to a maximum of 20mg/day in both groups. Study-dose change was based on a lack of improvement in PANSS negative symptoms.

Haloperidol
- Mean dose at end of study = 17.11(3.84) mg/day
- participants received additional blinded active benztropine mesylate 2mg PO b.i.d

Olanzapine
- Mean dose at end of study = 18.44(2.39) mg/day
- participants received benztropine mesylate placebo tablets.

| | |
|---|---|
| | For all participants, if significant EPS persisted despite benztropine, the dose of study drug was decreased. If this did not work, 2mg/day could be added in all cases. |
| **Outcomes** | **Leaving the study early:** Leaving due to any reason (non-adherence to study protocol) |
| | **Mental state (e.g. BPRS, PANSS, BDI):** Clinically significant response in mental state - defined as a 20% decrease of the PANSS negative subscale score |
| | **Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS; HAM-D |
| | **Adverse events:** Average score/change in specific adverse effects - SAS; AIMS |
| | **Cognitive functioning:** Average score/change in cognitive functioning Test batteries were created for: Executive functioning, Declarative verbal learning memory, Attention and processing speed, Motor functioning |
| | **Other:** Weight change, vital signs, laboratory values and prolactin levels |
| **Quality** | **1.1 The study addresses an appropriate and clearly focused question.:** Well covered |
| | **1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately |
| | **1.3 An adequate concealment method is used.:** Not addressed |
| | **1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered |
| | **1.5 The treatment and control groups are similar at the start of the trial.:** Adequately addressed |
| | **1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed |
| | **1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Adequately addressed |
| | **1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** <20% |
| | **1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Adequately addressed |
| | **1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not applicable |
| | **2.1 How well was the study done to minimise bias?: +** |

| | |
|---|---|
| **Study ID** | **OLIE2006 [TA: Study 128-305]** |
| **General info** | **Funding source:** Not mentioned |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |

**Type of analysis:** ITT - All randomised participants who had a baseline and at least one post-baseline efficacy evaluation, regardless of whether protocol inclusion/exclusion criteria were met.

- Evaluable population comprised randomised participants who had >=4 weeks of double-blind treatment and no major protocol deviations or violations.

**Blindness:** Double-blind

**Duration:** No. weeks of treatment 12

**Duration:** Median treatment duration - 12 weeks,

**Raters:** Not stated to be independent of treatment

**Design:** Multi-centre - 26 centres in Western Europe

**Number of people screened, excluded & reasons:** 143 participants screened, 20 excluded due to failure to fulfil inclusion criteria.

**Notes about study methods:** Randomisation procedure not reported

**Participants**

**Diagnosis:** Schizophrenia [% of sample] 100%

**Diagnostic tool:** Other DSM DSM-IIIR

**Inclusion criteria:**
- 18-64 years with a primary diagnosis of schizophrenia.
- Indication for maintenance therapy with antipsychotic medication.
- Women were either not of child-bearing potential or were practicing contraception.
- Baseline scores on the Negative PANSS subscale had to exceed the PANSS positive subscale by =>6

**Exclusion criteria:**
- Acute exacerbation of schizophrenia or psychosis 12 weeks prior to screening.
- history of psychosurgery
- severe medical illness

**Total sample size:** ITT population 122

**Total sample size:** No. randomised 123

**Total sample size:** Safety population 123

**Gender:** % female 36%

**Age:** Mean 39

**Age:** Range 21-65

**Ethnicity:** 100% white

**Setting:** Outpatient

**History:**
[Ziprasidone / Amisulpride]
Mean no. of previous hospitalisations: 4.3(7.5) / 7.3(9.8)
Mean duration of most recent hospitalisation (months): 4.0(12.4) / 1.6(2.7)
use of anticholinergic: 53% / 49%

**Baseline stats:**
[Ziprasidone / Amisulpride]
PANSS Negative subscale: 31.03 / 29.00

**Notes about participants:** - Participants underwent a minimum 3-day run-in period for screening procedures, including both psychiatric and medical evaluations.

- Permitted concomitant medications were lorazepam and temazapam. Anticholinergics and propranolol were gradually withdrawn (25% dosage reduction per week) but were reinstated, if needed.

**Interventions**

**Intervention - group 1.:** Ziprasidone (80-160 mg/day)
- Participants were started on 20 mg b.i.d.; after 2 days, dosage was increased to 40 mg b.i.d. At the investigator's discretion, dosage could be increased to 60 mg b.i.d. from week 2 onwards or to 80 mg b.i.d. from week 3 onwards.
- Mean dose 118mg/day
- n=60 (ITT n=59)

**Intervention - group 2.:** Amisulpride (100-200 mg/day)
- The starting dosage was 50 mg b.i.d. This could be increased to 150mg per day from week 2 onwards and to 100 mg b.i.d. from week 3 onwards, according to clinical response.
- Mean dose: 144.7 mg/day
- n=63

**Notes about the interventions:** Doses were administered in three capsules approximately 12 hours apart.

**Outcomes**

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Leaving the study early:** Leaving because of adverse effects

**Global state & service outcomes (e.g. CGI):** Clinically significant response in global state: CGI - responder was defined as having an observed score of 1-2 on the CGI-I scale at the last observation.

**Global state & service outcomes (e.g. CGI):** Average score/change in global state - CGI; GAF

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - BPRS; PANSS Negative subscale

**Mental state (e.g. BPRS, PANSS, BDI):** Clinically significant response in mental state - PANSS - responder defined as having at least a 20% decrease in PANSS negative subscale score at the last observation relative to baseline.

Responder rates based on 30-50% decrease in PANSS Negative scores were also calculated.

**Adverse events:** Number of people with general adverse effects

**Adverse events:** Number of people with specific adverse effects

**Adverse events:** Average score/change in specific adverse effects - SAS; BAS; AIMS; MDBS

**Other:** - ECGs, BMI, and clinical laboratory tests including blood cell counts, blood biochemistry and urinalysis were also conducted.
- Clinically significant changes in BMI (defined as a change of >=7% were also reported.

**Quality**

**1.1 The study addresses an appropriate and clearly focused question.:** Well covered

**1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately

**1.3 An adequate concealment method is used.:** Not addressed

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered

**1.5 The treatment and control groups are similar at the start of the trial.:** Adequately addressed

**1.6 The only difference between groups is the treatment under investigation.:** Not addressed

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** 20-50%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Well covered

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not addressed

**2.1 How well was the study done to minimise bias?:** +

**Study ID**

**RIEDEL2005**

**General info**

**Funding source:** Any pharmaceutical industry support

**Published or unpublished data?:** Published

**Method**

**Type of study:** Individual randomised trial

**Type of analysis:** Completer

**Type of analysis:** ITT All patients randomised with baseline data and at least one post-baseline measure

**Type of analysis:** LOCF

**Blindness:** Double-blind

**Duration:** Mean duration (for each group) - Mean treatment duration was 66.1 days in the quetiapine group and 62.7 days in the risperidone group.

**Duration:** No. weeks of treatment 12

**Raters:** Not stated to be independent of treatment

**Number of people screened, excluded & reasons:** - Upon entering the study, a thorough medical and psychiatric history was carried out.
- No participants were excluded after screening

**Notes about study methods:** Randomisation procedure not reported

**Participants**

**Diagnosis:** Schizophrenia [% of sample] 100

**Diagnostic tool:** DSM-IV

**Diagnostic tool:** ICD-10

**Inclusion criteria:**
- CGI score >=4
- Presenting with predominantly primary negative symptoms according to PANSS
- PANSS negative subscale score >=21 and at least 1 point greater than their positive subscale score

**Exclusion criteria:**
- drug or alcohol misuse/dependence
- suicidal tendencies
- laboratory or ECG/ EEG abnormalities (blood or urine values outside standard range by more than 20%)
- pregnancy or lactation
- significant medical history (brain surgery, unstable somatic conditions, HIV +)
- treatment with clozapine within 4 weeks of enrolment.

**Total sample size:** ITT population - ITT population not reported. Number of completers for each intervention group reported:
[Quetiapine / Risperidone]
No. of completers: 13 / 12

**Total sample size:** No. randomised 44

**Gender:** % female 39%

**Age:** Mean
[Quetiapine / Risperidone]
Age: 30.6(10.9) / 39.3(12.3)
*statistically significant difference between the two groups at baseline.

**Setting:** Outpatient

**Setting:** Inpatient

**History:**
[Quetiapine / Risperidone]
Age of onset: 25.3(10.5) / 36.9(17.7)
Duration of illness: 5.4(7.5) / 2.5(12.7)

**Baseline stats:**
[Quetiapine / Risperidone]
PANSS: 103.4(16.4) / 97.8(16.9)
SANS: 66.7(20.6) / 51.7(21.1)
SAS: 0.2(1.1) / 0.5(1.3)

**Interventions**

**Intervention - group 1.:** Quetiapine,50-600 mg/day, n=22

**Intervention - group 2.:** Risperidone, 2-6mg/day, n=22

**Notes about the interventions:** Each participant underwent a 2 day washout period before beginning the trial.

Quetiapine:
50mg on day 1, 100 mg on day 2, and then daily 100 mg increments to 600 mg/day on day 7. Thereafter, the dose of study medication was adjusted according to the clinical judgement of the investigators, with the maximum dose allowed: 800mg/day
- Mean dose: 589.7mg/day

Risperidone:
initiated at 2 mg/day on days 1 and 2, increasing to 4 mg/day on days 3–5 and 6 mg/day on days 6 and 7. Thereafter, the dose of study medication was adjusted according to the clinical judgement of the investigators with the maximum dose allowed: 8 mg/day
-Mean dose: 4.9mg/day

-Besides standard clinical management, no additional psychotherapy was performed.

-Both risperidone and quetiapine were packed in lactose capsules containing 100 mg quetiapine or 1mg risperidone, with identical size and appearance to maintain blindness.

-Lorazepam (≤ 4 mg/day); zopiclone (≤ 15 mg/day); Biperiden hydrochloride (≤ 8 mg/day) were all allowed throughout the trial.

**Outcomes**

**Leaving the study early:** Leaving because of adverse effects

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

| | |
|---|---|
| | **Global state & service outcomes (e.g. CGI):** Average score/change in global state - CGI |
| | **Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS; SANS |
| | **Adverse events:** Number of people with general adverse effects |
| | **Adverse events:** Average score/change in specific adverse effects - SAS |
| | **Adverse events:** Number of people with specific adverse effects |
| | **Other:** ECGs, assessment of vital signs, weight gain, serum prolactin levels, cortisol levels. |
| **Quality** | **1.1 The study addresses an appropriate and clearly focused question.:** Well covered |
| | **1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately |
| | **1.3 An adequate concealment method is used.:** Not addressed |
| | **1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered |
| | **1.5 The treatment and control groups are similar at the start of the trial.:** Well covered |
| | **1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed |
| | **1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered |
| | **1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** 20-50% |
| | **1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Well covered |
| | **1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not addressed |
| | **2.1 How well was the study done to minimise bias?: +** |

| | |
|---|---|
| **Study ID** | **RUHRMANN2007** |
| **General info** | **Funding source:** Any pharmaceutical industry support |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of study:** Individual randomised trial (Noninferiority/equivalence) |
| | **Type of analysis:** LOCF |
| | **Type of analysis:** ITT - subjects with at least one post-randomisation observation.<br>Valid for efficacy sample - as used for the primary outcome parameter and included subjects with a minimum treatment duration of 8 weeks. |

Safety population - all patients with at least one study drug administration after randomisation.

**Type of analysis:** Completer

**Blindness:** Double-blind

**Duration:** No. weeks of treatment up to 25 weeks

**Raters:** Not stated to be independent of treatment

**Design:** Multi-centre - 27 centres in Germany, 3 in Austria

**Number of people screened, excluded & reasons:** Not reported

**Notes about study methods:** Randomisation procedure not reported.

**Participants**

**Diagnosis:** Schizophrenia [% of sample] 100% (ICD-10 diagnosis F20.0–F20.3, F20.5–F20.9)

**Diagnostic tool:** ICD-10

**Inclusion criteria:**
- aged 18
- diagnosis of schizophrenia according to ICD-10 criteria for >=2 years
- >=3 PANSS negative syndrome subscale scoring ≥4 points;
- stable clinical state, e.g. maintenance treatment had been started or that consideration of a change in stable medication was not due to any acute exacerbation of positive symptoms.

**Exclusion criteria:**
- contraindication to treatment with, or hypersensitivity to any of the study drugs
- dependence on alcohol or illegal drugs according to ICD-10 criteria;
- concomitant treatment with lithium, carbamazepine
other mood stabilisers or other psychopharmacological drugs - treatment with flupentixol or risperidone within 4 weeks preceding study
- history of treatment with clozapine (to avoid inclusion of treatment-resistant cases);
- concurrent clinically relevant physical conditions;
- acute suicidal ideation;
- participation in a clinical study
- pregnant or breast-feeding females, or those of child bearing potential not using a medically approved contraceptive.

**Total sample size:** Safety population 153

**Total sample size:** ITT population 144

**Total sample size:** No. randomised 153

**Gender:** % female 37.5% (Details for the ITT population only)

**Age:** Mean 40.39(11.98)

**Ethnicity:** Not reported

**Setting:** Inpatient

**Setting:** Outpatient

**History:**
[Flupentixol / Risperidone]
Years since diagnosis: 11.28(9.98) / 11.50(10.07)
Number of previous episodes: 4.87(4.48) / 4.73(4.38)

**Baseline stats:**
[Flupentixol / Risperidone]
PANSS neg: 27.67(5.44) / 27.65(5.40)
PANSS pos: 17.72(4.47) / 14.65(5.45)
PANSS gen: 40.90(10.977) / 39.47(9.93)

The above scores are based on a 3-factor solution used in the paper.

**Notes about participants:**
All participants belonged either to the 'minus' or to the 'mixed' subtype assuring a significant level of negative symptoms.

Treatment with antipsychotics before inclusion in to the study.
[Flupentixol / Risperidone]
Butyrophenone per os: 32 / 24
Phenothiazine per os: 11 / 8
Haloperidol depot: 3 / 6
Zuclopentixol depot: 3 / 2
Olanzapine: 9 / 11
Amisulpride: 3 / 3
Sertindole: 0 / 2
Others: 8 / 9
No current pre-study medication: 6 / 6
Unknown: 1 / 6

**Interventions**

**Intervention - group 1.:** Flupentixol: 4-12 mg/day, n=76

**Intervention - group 2.:** Risperidone, 2-6 mg/day, n = 77

**Notes about the interventions:** The first week was a run-in phase, previous medication was washed out and study medication was given at the minimal dosage.
- Thereafter, dosing for both study drugs was flexible within the specified ranges.
- Medication was administered in identical capsules containing either 2 mg of flupentixol or 1 mg of risperidone. Drugs were

given twice a day (day one 2×1, day 2 up to 2×2, from day 3 up to 2×3 capsules).
- The only permissible concomitant medications were anticholinergic agents (biperiden) and short-term benzodiazepines and non-benzodiazepine hypnotics (for sleep induction).

**Outcomes**

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Leaving the study early:** Leaving because of adverse effects

**Global state & service outcomes (e.g. CGI):** Relapse - Defined as a deterioration of >=10 points on BPRS

**Global state & service outcomes (e.g. CGI):** Average score/change in global state CGI

**Mental state (e.g. BPRS, PANSS, BDI):** Clinically significant response in mental state Defined by a standard criterion as a reduction of baseline scores >=20% and by a strong criterion as a reduction of >=50%

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state PANSS - conducted a factor analysis, with resulting 3 and 5-factor models, MADRS

**Adverse events:** Number of people with general adverse effects

**Adverse events:** Average score/change in specific adverse effects ESRS

**Adverse events:** Number of people with specific adverse effects Table reporting all AEs experienced by >5% of the study population.

**Other:** BMI, vital signs including diastolic blood pressure and heart rate

**Quality**

**1.1 The study addresses an appropriate and clearly focused question.:** Well covered

**1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately

**1.3 An adequate concealment method is used.:** Not addressed

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered

**1.5 The treatment and control groups are similar at the start of the trial.:** Well covered

**1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Adequately addressed

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** 20-50%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Well covered

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Adequately addressed

**2.1 How well was the study done to minimise bias?: +**

| Study ID | SIROTA2006 |
|---|---|
| General info | **Funding source:** Any pharmaceutical industry support |
| | **Published or unpublished data?:** Published |
| Method | **Type of study:** Individual randomised trial |
| | **Type of analysis:** LOCF |
| | **Type of analysis:** ITT all those patients who were randomised with baseline data and had at least one post-baseline measurement |
| | **Blindness:** Only raters blind |
| | **Duration:** No. weeks of treatment 12 |
| | **Raters:** Independent of treatment |
| | **Design:** Single-centre Israel |
| | **Number of people screened, excluded & reasons:** screening method not reported |
| | **Notes about study methods:** randomisation procedure not reported |
| Participants | **Diagnosis:** Schizophrenia [% of sample] 100% |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:**<br>- primary enduring negative symptoms according to Carpenter's Criteria for the Deficit Syndrome.<br>-negative symptoms not adequately responded to previous medication, defined as a lack of response to at least two conventional antipsychotics at a dose of 400-600mg chlorpromazine equivalents for a period of 4-6 weeks<br>- PANSS negative subscale score >15<br>- SANS total >60 |
| | **Exclusion criteria:**<br>- concurrent Axis 1 SAM-IV disorder<br>- history of seizure disorder, or any clinically significant medical condition that would interfere with evaluations of efficacy or tolerability.<br>- pregnancy<br>- use of depot antipsychotic within one dosing interval<br>- participation in another investigational drug trial within 30 days on enrolment |
| | **Total sample size:** No. randomised 40 |
| | **Total sample size:** ITT population 40 |
| | **Gender:** % female 20% |
| | **Age:** Mean 37 |

**Ethnicity:** Not reported

**Setting:** Inpatient

**History:**
[Quetiapine / Olanzapine]
Mean duration of illness, years: 15.9(9.1) / 13.3(7.4)

**Baseline stats:** Baseline not reported (Change from baseline used in the analysis)

**Notes about participants:**
[Quetiapine / Olanzapine]
Previous antipsychotic, n(%)
haloperidol: 5(26.3) / 5(23.8)
perphenazine: 4(21.0) / 4(19.0)
sulpiride: 1(5.2) / 2(9.5)
zuclopenthixol: 3(15.7) / 3(14.2)
risperidone: 6 (31.5) / 7(33.3)

**Interventions**

**Intervention - group 1.:** Quetiapine, 200-800 mg/day, n=19

**Intervention - group 2.:** olanzapine, 5-20mg/day, n=21

**Notes about the interventions:**
Quetiapine
- 50mg/d on day 1, 100mg/d on day 2, 200mg/d on days 3-4 and 300mg/d on days 5-7. Thereafter patients received 400mg/d for 2 weeks followed by 600mg/d for 6 weeks.
- For patients who did not respond sufficiently to 600mg/d, dose increased to 800mg/d until the end of study.

Olanzapine
- 5mg/d on days 1-5, 10mg/d on days 6-10. Thereafter 15mg/d for 4 weeks.
- For patients who did not respond sufficiently to 15 mg/d, dose increased to 20mg/d until the end of the study

Patients in both groups were flexibly dosed throughout the study according to clinical response. Although patients were not receiving any other antipsychotic, biperiden was allowed for the management of EPS

**Outcomes**

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS; SANS

**Adverse events:** Number of people with general adverse effects

**Adverse events:** Number of people with specific adverse effects - Lists AEs occurring in >=7% of patients,

**Adverse events:** Average score/change in specific adverse effects - SAS; BAS; AIMS

**Other:** weight gain; laboratory measures including haematology, chemistry, thyroid and urinalysis; ECG

**Quality**

**1.1 The study addresses an appropriate and clearly focused question.:** Well covered

**1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately

**1.3 An adequate concealment method is used.:** Not addressed

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Poorly addressed

**1.5 The treatment and control groups are similar at the start of the trial.:** Not reported adequately

**1.6 The only difference between groups is the treatment under investigation.:** Not addressed

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** <20%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Well covered

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not applicable

**2.1 How well was the study done to minimise bias?:** +

**References of included studies (update)**

**HERTLING2003**

Hertling,I.; Philipp,M.; Dvorak,A.; Glaser,T.; Mast,O.; Beneke,M.; Ramskogler,K.; Saletu,Zyhlarz G.; Walter,H.; Lesch,O.M. (2003) Flupenthixol versus risperidone: subjective quality of life as an important factor for compliance in chronic schizophrenic patients. *Neuropsychobiology.* 47: 37 - 46.

**KINON2006B**

Kinon,B.J.; Noordsy,D.L.; Liu-Seifert,H.; Gulliver,A.H.; scher-Svanum,H.; Kollack-Walker,S. (2006B) Randomized, double-blind 6-month comparison of olanzapine and quetiapine in patients with schizophrenia or schizoaffective disorder with prominent negative symptoms and poor functioning. *Journal of Clinical Psychopharmacology.* 26(**5**): 453 - 461.

**LINDENMAYER2007**

Lindenmayer,J.P.; Khan,A.; Iskander,A.; Abad,M.T.; Parker,B. (2007) A randomized controlled trial of olanzapine versus haloperidol in the treatment of primary negative symptoms and neurocognitive deficits in schizophrenia. *Journal of Clinical Psychiatry* 68: 368 - 379.

**OLIE2006 [TA: Study 128-305]**

Olie,J.P.; Spina,E.; Murray,S.; Yang,R. (2006) Ziprasidone and amisulpride effectively treat negative symptoms of schizophrenia: results of a 12-week, double-blind study. *International Clinical Psychopharmacology.* 21: 143 - 151.

**RIEDEL2005**

*Riedel,M.; Muller,N.; Strassnig,M.; Spellmann,I.; Engel,R.R.; Musil,R.; Dehning,S.; Douhet,A.; Schwarz,M.J.; Moller,H.J. (2005) Quetiapine has equivalent efficacy and superior tolerability to risperidone in the treatment of schizophrenia with predominantly negative symptoms. *European Archives of Psychiatry and Clinical Neuroscience.* 255(**6**): 432 - 437.

Riedel, M., Spellmann, I., Strassnig, M., et al. (2007) Effects of risperidone and quetiapine on cognition in patients with schizophrenia and predominantly negative symptoms. *European Archives of Psychiatry and Clinical Neuroscience.* 257: 360-70.

**RUHRMANN2007**

Ruhrmann,S.; Kissling,W.; Lesch,O.M.; Schmauss,M.; Seemann,U.; Philipp,M. (2007) Efficacy of flupentixol and risperidone in chronic schizophrenia with predominantly negative symptoms. *Progress in Neuro-Psychopharmacology and Biological Psychiatry.* 31(**5**): 30.

**SIROTA2006**

Sirota,P.; Pannet,I.; Koren,A.; Tchernichovsky,E. (2006) Quetiapine versus olanzapine for the treatment of negative symptoms in patients with schizophrenia. *Human Psychopharmacology.* 21(**4**): 227 - 234.

## Augmentation of antipsychotic medication with another antipsychotic

### Characteristics of included studies (update)

| Study ID | CHANG2008 |
|---|---|
| General info | **Funding source:** Pharmaceutical industry |
| | **Funding source:** Non-industry support |
| | **Published or unpublished data?:** Published |
| Method | **Type of study:** Individual randomised trial |
| | **Type of analysis:** LOCF |
| | **Type of analysis:** ITT |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment 8 |
| | **Design:** Single-centre |
| Participants | **Diagnosis:** Schizophrenia [% of sample] 100 |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:**<br>- Age 18-65 years;<br>- Documented treatment failure prior to clozapine treatment; clozapine treatment >1 year with at least 8 weeks of a stable daily dose of 400 mg or more, unless compromised by AEs; no change in clozapine daily dose or other concomitant medication for more than 3 months; either BPRS >= 35 or >2 SANS global rating item scores of at least 3. |
| | **Exclusion criteria:**<br>- Substance dependence;<br>- prior treatment failure with aripiprazole. |
| | **Total sample size:** No. randomised 62 |
| | **Gender:** % female 21.3% |
| | **Age:** Mean CLZ+ARI = 33.2; CLZ+PLB = 31.7 |
| | **Ethnicity:** All "ethnically identical Koreans" |
| | **Setting:** Inpatient |

| | |
|---|---|
| | **Baseline stats:** BPRS total: CLZ+ARI = 47.6 (9.3); CLZ+PLB = 48.5 (10.5) |
| **Interventions** | **Intervention - group 1.:** CLZ+ARI, 15.5 (7.1) mg/d for ARI, n=30 |
| | **Intervention - group 2.:** CLZ+PLB, 17.0 (7.4) for PLB, n=32 |
| **Outcomes** | **Leaving the study early:** Leaving because of adverse effects |
| | **Leaving the study early:** Leaving due to any reason (non-adherence to study protocol) |
| | **Global state & service outcomes (e.g. CGI):** Average score/change in global state - CGI-S |
| | **Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - BPRS, SANS, MADRS |
| | **Adverse events:** Average score/change in specific adverse effects |
| **Quality** | **1.1 The study addresses an appropriate and clearly focused question.:** Well covered |
| | **1.2 The assignment of subjects to treatment groups is randomised.:** Well covered |
| | **1.3 An adequate concealment method is used.:** Well covered |
| | **1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered |
| | **1.5 The treatment and control groups are similar at the start of the trial.:** Well covered |
| | **1.6 The only difference between groups is the treatment under investigation.:** Well covered |
| | **1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered |
| | **1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** <20% |
| | **1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Well covered |
| | **1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not applicable |
| | **2.1 How well was the study done to minimise bias?: ++** |

| | |
|---|---|
| **Study ID** | **FREUDENREICH2007** |
| **General info** | **Funding source:** Non-industry support |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** ITT All randomised participants |
| | **Type of analysis:** LOCF |

**Blindness:** Double-blind

**Duration:** No. weeks of treatment 6

**Raters:** Not stated to be independent of treatment

**Design:** Single-centre - Urban mental health clinic

**Number of people screened, excluded & reasons:** 123 patients were approached, 56 declined to participate in the study and 39 were excluded due to ineligibility. A further 4 patients were eliminated after screening for failing to reach the symptom severity criterion

**Notes about study methods:** An independent research pharmacy randomised the participants in blocks of 10

**Participants**

**Diagnosis:** Schizophrenia [% of sample] 100%

**Diagnostic tool:** DSM-IV

**Inclusion criteria:**
- stable residual psychiatric symptoms defined by PANSS score >60
- failed at least 2 previous trials of antipsychotics prior to clozapine
- treated with clozapine for >=6months at a stable dose for >=8 weeks
- clozapine plasma levels >=200ng/mL unless the clozapine dose necessary to achieve that level was not tolerated.

**Exclusion criteria:**
- active substance use disorder
- unstable medical illness
- suicidal ideation
- any cognitive disorder (including mental retardation) or developmental disorder

**Total sample size:** No. randomised 24

**Total sample size:** ITT population 24

**Gender:** % female 12.5%

**Age:** Range 27-55

**Age:** Mean 42.3

**Ethnicity:** not reported

**Setting:** Outpatient

**History:** on average, age of first hospitalisation = 22.1 (range 18-31) and illness duration = 20.6 years (range 3-34)

**Baseline stats:**
[Risperidone / placebo]
PANSS total: 72.4(11.9) / 73.5(11.0)
SANS: 35.5(12.8) / 36.3(11.0)

SARS: 3.2(2.2) / 3.8(2.7)
BARS: 0.2(0.4) / 0.2(0.4)
AIMS: 1.0(2.0) / 0.8(1.6)

**Interventions** **Intervention - group 1.:** Risperidone, 4mg/day, n=11

**Intervention - group 2.:** placebo, n=13

**Notes about the interventions:** Treatment period was preceded by a 2-week single-blind placebo lead-in period to eliminate potential placebo-responders.

An independent research pharmacy prepared matching capsules that contained either 1mg risperidone or placebo. Participants received 1 capsule twice daily for 3 days, then 2 capsules twice daily for the remainder.

Ancillary stable psychotropics were allowed.

**Outcomes** **Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Mental state (e.g. BPRS, PANSS, BDI):** Clinically significant response in mental state - PANSS - number with a 20% improvement

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS; CDSS; SANS

**Adverse events:** Number of people with general adverse effects - Mentions SAFTEE was performed, but does not give averages, instead reports a general picture of results.

**Adverse events:** Average score/change in specific adverse effects - BAS; AIMS; SARS

**Other:** laboratory values including prolactin levels, and mean plasma levels for risperidone

**Quality** **1.1 The study addresses an appropriate and clearly focused question.:** Well covered

**1.2 The assignment of subjects to treatment groups is randomised.:** Adequately addressed

**1.3 An adequate concealment method is used.:** Well covered

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered

**1.5 The treatment and control groups are similar at the start of the trial.:** Adequately addressed

**1.6 The only difference between groups is the treatment under investigation.:** Not addressed

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** <20%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Well covered

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not applicable

**2.1 How well was the study done to minimise bias?: +**

| | |
|---|---|
| **Study ID** | **HONER2006** |
| **General info** | **Funding source:** Non-industry support |
| | **Funding source:** Any pharmaceutical industry support |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** ITT not defined |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment 8 |
| | **Duration:** Length of follow-up optional 18 week open-label augmentation with risperidone |
| | **Raters:** Independent of treatment |
| | **Design:** Multi-centre - 7 sites in Canada, Germany, China and the UK |
| | **Number of people screened, excluded & reasons:** 595 patients were assessed for eligibility, 458 (77%) did not meet the inclusion criteria, 69(12%) declined to participate. A total of 71 participants were enrolled, 2 of whom withdrew consent prior to randomisation. 1 participant improved during the 7-day single-blind period and no longer met inclusion criteria for randomisation, leaving a total of 68 randomised participants. |
| | **Notes about study methods:** Randomisation was performed according to a computer-generated schedule with a permuted-block design. The fixed block size was 4 participants. The person generating the randomisation schedule was not involved in determining the participants' eligibility, administering treatment, or determining outcome. The participants were randomly assigned in sequence at each site. |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 93% |
| | **Diagnosis:** Other schizophrenia related [%] schizoaffective disorder - 7% |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:**<br>- diagnosis of schizophrenia or schizoaffective disorder according to DSM-IV criteria<br>- aged 18-65<br>- treatment with clozapine for the indication of poor response to other antipsychotic agents; treatment >=12 weeks at a stable dose >=400mg/day, unless the size of the dose was limited by side effects<br>- PANSS total >=80, CGI score >=4,and a SOFAS score <=40 |

**Exclusion criteria:**
- clinically significant alcohol or substance abuse in the previous 3 months
- developmental disability
- current treatment with clozapine for the primary indication of movement disorder or of intolerable side effects from other medications, or previous treatment with clozapine augmented with risperidone.

**Total sample size:** No. randomised 68

**Total sample size:** ITT population not clearly reported

**Gender:** % female 26%

**Age:** Mean 37.2(10.0)

**Ethnicity:** white - 72%
Black - 1%
Asian - 18%
Another racial or ethnic group - 9%

**Setting:** Outpatient

**Setting:** Inpatient

**History:**
[Risperidone / placebo]
Type of care, no:
Inpatient: 13 / 13
outpatient: 21 / 21
Age at first hospitalisation, year: 22.1(6.7) / 21.5(4.1)
Duration of illness, year: 16.9(11.2) / 13.0(9.0)
Previous hospitalisations: 4.9(3.3) / 5.9(5.2)

**Baseline stats:**
[Risperidone / Placebo]
CGI-S n(%)
Moderate: 4(12) / 10(29)
Marked: 14(41) / 18(53)
Severe: 13(38) / 5(15)
Extreme: 3(9) / 1(3)
SOFAS score: 32.2(7.4) / 35.0(7.5)
PANSS total: 102.5(14.6) / 97.8(12.4)
verbal working-memory index: 0.09(0.83) / -0.10(0.85)

**Notes about participants:**
[Risperidone / Placebo]
Different antipsychotic drugs used in past 5 years: 3.5(2.1) / 2.9(1.8)
clozapine dose, mg/day: 494(168) / 487(135)
Duration of clozapine treatment: 209(226) / 111(161)
Received risperidone before clozapine treatment, no(%): 20(59) / 21(62)

**Interventions** **Intervention - group 1.:** Risperidone, 3mg/day, n=34

**Intervention - group 2.:** placebo, n=34

**Notes about the interventions:**
- all participants entered a one-week single-blind placebo augmentation phase prior to randomisation. On day 7, patients with an improvement in the overall PANSS score >=20% were withdrawn from the study
- Patients were required to discontinue any antipsychotic drugs other than clozapine, any mood-stabilising or antidepressant drugs, and any anticonvulsant drugs for at least 2 weeks before the study (except for fluoxetine and ECT, which were discontinued for >= four weeks). Concomitant medications for stable medical conditions were permitted.

Risperidone
- administered as 1-mg tablets, dose was increased to 3mg/day over the first 15 days. The investigators were allowed to decrease the dose by one tablet per day if the side effects were intolerable.

**Outcomes** **Leaving the study early:** Leaving because of adverse effects

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Global state & service outcomes (e.g. CGI):** Average score/change in global state - CGI

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS

**Mental state (e.g. BPRS, PANSS, BDI):** Clinically significant response in mental state - PANSS - participants with a >=20% reduction in the total score were classified as having a response.

**Adverse events:** Average score/change in specific adverse effects - ESRS; BAS

**Adverse events:** Number of people with specific adverse effects. Reports the number of participants withdrawn due to serious adverse effects UKU side-effect rating scale

**Adverse events:** Number of people with general adverse effects

**Other:** Weight, waist circumference, fasting blood glucose, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, white cell counts.

**Quality** **1.1 The study addresses an appropriate and clearly focused question.:** Well covered

**1.2 The assignment of subjects to treatment groups is randomised.:** Well covered

**1.3 An adequate concealment method is used.:** Well covered

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered

**1.5 The treatment and control groups are similar at the start of the trial.:** Well covered

**1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** <20%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Well covered

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not addressed

**2.1 How well was the study done to minimise bias?:** ++

| **Study ID** | **JOSIASSEN2005** |
|---|---|
| **General info** | **Funding source:** Any pharmaceutical industry support |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** Completer – all participants completed the study |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment - 12 |
| | **Raters:** Independent of treatment |
| | **Design:** Multi-centre - details not provided |
| | **Number of people screened, excluded & reasons:** details not reported |
| | **Notes about study methods:** randomisation procedure not reported |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] % not reported |
| | **Diagnosis:** Other schizophrenia related [%] schizoaffective - % not reported |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:**<br>- DSM-IV diagnosis of schizophrenia or schizoaffective disorder;<br>- aged 20–65 |

- before treatment with clozapine, documented treatment failure after two antipsychotics were administered for an adequate duration in a sufficient dose (>=6 weeks of 1000 mg/day of chlorpromazine equivalents)
- failure to show a satisfactory clinical response to an adequate trial of clozapine (>=3 months of at least 600 mg/day of oral clozapine or a plasma drug level >= 350 ng/ml)
- persistent psychotic symptoms, evidenced by either BPRS total >=45, or a rating of moderately ill (4 or more) on >=2 of the 4 BPRS positive symptom items

**Total sample size:** No. randomised 40

**Gender:** % female 12.5%

**Age:** Mean 40

**Ethnicity:** details not reported

**Setting:** Inpatient

**Setting:** Outpatient

**History:**
[risperidone / placebo]
Age of symptom onset: 18.4(3.1) / 17.7(5.3)
Age of first hospitalisation: 20.4(3.8) / 19.7(5.3)
Duration of illness, years: 21.8(7.0) / 22.4(11.6)

**Baseline stats:**
[risperidone / placebo]
BPRS total: 48.8(9.2) / 47.1(13.3)
GCI: 5.2(1.1) / 5.2(1.7)
SANS: 68.4(27.5) / 71.5(30.9)
SAS: 0.15(0.7) / 0.75(1.3)

**Notes about participants:**
[risperidone / placebo]
initial clozapine dose, mg/day: 528.8(166.7) / 402.5(102.9)

**Interventions** **Intervention - group 1.:** risperidone, up to 6mg/day, n=20

**Intervention - group 2.:** placebo, n=20

**Notes about the interventions:**
All participants underwent a 4-week, clozapine run-in phase during which time they had to remain on a stable dose of clozapine for at least 4 weeks. Baseline doses of clozapine were established by treating psychiatrists and remained stable throughout the study. Participants were then assigned to receive either risperidone or matching placebo. All participants remained in their current living arrangements without any study-related modifications to their daily routines

| | |
|---|---|
| | Risperidone<br>- started at 1mg/day, with planned increase to 1 or 2mg/day on day 4, to 2 or 3mg/day on day 8, to 4mg/day on day 21, and to 6mg/day on day 22.<br>- patients judged by their treating psychiatrist to be unable to tolerate the dose escalation scheme because of adverse events were maintained at their maximum tolerated dose for the remainder for the study |
| **Outcomes** | **Leaving the study early:** Leaving due to any reason (non-adherence to study protocol). Reports that all participants completed the study |
| | **Mental state (e.g. BPRS, PANSS, BDI):** Clinically significant response in mental state >=20% reduction in BPRS total score |
| | **Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - BPRS; SANS |
| | **Adverse events:** Average score/change in specific adverse effects - SAS |
| | **Other:** Paper mentions briefly adverse events, plasma levels and white blood counts but does not provide any usable data. |
| **Quality** | **1.1 The study addresses an appropriate and clearly focused question.:** Well covered |
| | **1.2 The assignment of subjects to treatment groups is randomised.:** Not reported adequately |
| | **1.3 An adequate concealment method is used.:** Not addressed |
| | **1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered |
| | **1.5 The treatment and control groups are similar at the start of the trial.:** Poorly addressed |
| | **1.6 The only difference between groups is the treatment under investigation.:** Well covered |
| | **1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Adequately addressed |
| | **1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** <20% |
| | **1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Not applicable - all participants completed study |
| | **1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not reported adequately |
| | **2.1 How well was the study done to minimise bias?:** + |

| | |
|---|---|
| **Study ID** | **SHILOH1997** |
| **General info** | **Funding source:** Not mentioned |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |

**Blindness:** Double-blind

**Duration:** No. weeks of treatment - 10

**Design:** Single-centre

**Participants** **Diagnosis:** Schizophrenia [% of sample] 100

**Diagnostic tool:** DSM-IV

**Inclusion criteria:**
- failure to respond to at least three types of typical antipsychotics at adequate therapeutic doses, given for a period of not less than 6 weeks each.
- exhibiting a partial and unsatisfactory response to clozapine following at least 12 weeks of treatment in an adequate dose.
- Partial/unsatisfactory response to clozapine was defined as a score of at least 25 on the BPRS and inability to function as an outpatient.

To ensure that the response to clozapine had reached a plateau, the last 5 weeks, at least, had to be characterised by a stable, unchanged clinical state (change in BPRS score <5%).

**Total sample size:** No. randomised 28

**Gender:** % female 32.14

**Age:** Mean CLZ+SUL = 40.3 years; CLZ+PLB = 37.1 years

**Setting:** Inpatient

**Baseline stats:** BPRS: CLZ+SUL = 41.9 (12.2); CLZ+PLB = 43.5 (9.7)

**Interventions** **Intervention - group 1.:** Clozapine + sulpiride, 600 mg/d of sulpiride, n=16

**Intervention - group 2.:** Clozapine + placebo, 600 mg/d of placebo, n=12

**Outcomes** **Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - BPRS, SAPS, SANS, HDRS

**Mental state (e.g. BPRS, PANSS, BDI):** Clinically significant response in mental state

**Adverse events:** Average score/change in specific adverse effects

**Adverse events:** Number of people with specific adverse effects

**Quality** **1.1 The study addresses an appropriate and clearly focused question.:** Well covered

**1.2 The assignment of subjects to treatment groups is randomised.:** Adequately addressed

**1.3 An adequate concealment method is used.:** Not reported adequately

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Adequately addressed

**1.5 The treatment and control groups are similar at the start of the trial.:** Adequately addressed

**1.6 The only difference between groups is the treatment under investigation.:** Adequately addressed

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** <20%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Adequately addressed

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not applicable

**2.1 How well was the study done to minimise bias?:** +

| **Study ID** | **YAGCIOGLU2005** |
|---|---|
| **General info** | **Funding source:** Any pharmaceutical industry support |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** LOCF Mixed model was used in preference to LOCF (follow-up paper reports that the mixed model included all participants who were randomised and included data on patients who did not complete the study period) |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment 6 |
| | **Raters:** Independent of treatment |
| | **Design:** Multi-centre - 2 sites |
| | **Number of people screened, excluded & reasons:** 27 patients were excluded due to exclusion criteria |
| | **Notes about study methods:** Randomisation was planned by one of the unblinded investigators prior to the initiation of the study in a 1:1 ratio, and a pre-assigned random sequence was determined for each site. The patients arriving at each site were assigned the study medication according to this sequence in order with their enrolment |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 100% |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:**<br>- diagnosis of schizophrenia or schizoaffective disorder who had been receiving clozapine treatment (300-900mg/day) for >=6 months<br>- previous failure to respond adequately, had persistent positive symptoms, to at least 2 trials of adequate duration and dose of antipsychotic drugs other than clozapine.<br>- level of positive symptoms stable by clinical criteria reported in written notes for >=3 months. |

- PANSS total >=72, and >=3 on any 1 of the PANN POS items
- CGI-S score >= 4

**Exclusion criteria:**
- concomitant mood stabilisers, including lithium carbonate, antidepressants, and/or antipsychotic medication other than clozapine
- history of intolerance to risperidone for reasons other than EPS, or who had EPS that were not adequately responsive to the addition of anticholinergic medication when receiving <=6mg/day risperidone
- alcohol or substance dependence within 3 months of study entry

**Total sample size:** No. randomised 30

**Gender:** % female 33%

**Age:** Mean 33

**Ethnicity:** Not reported

**Setting:** Outpatient

**Setting:** Inpatient

**History:**
[risperidone / placebo]
Inpatient/outpatient: 5/11 / 1/13
diagnosis, n:
disorganised: 1 / 0
paranoid: 10 / 6
catatonic: 0 / 0
undifferentiated: 1 / 4
residual: 4 / 4
Age at onset: 20.9(4.5) / 21.2(3.7)
Duration of illness: 14.34(9.1) / 9.8(5.9)
total no. of hospitalisations: 3.6(2.5) / 1.5(1.7)

**Baseline stats:**
[risperidone / placebo]
PANSS total, mean. (SE): 77.4(1.65) / 77.4(1.78)
PANSS POS: 17.9(0.53) / 17.9(0.56)
CGI-S: 4.5(0.12) / 4.5(0.13)
CDS: 2.9(0.50) / 2.4(0.51)
GAF: 48.5(1.3) / 48.4(1.4)
QLS total: 46.4(2.14) / 45.9(2.29)

SAS: 12.4(0.37) / 12.2(0.40)
BAS: 0.37(0.15) / 0.36(0.16)
AIMS: 1.4(0.21) / 1.5(0.23)

**Notes about participants:**
[risperidone / placebo]
Duration of clozapine, months: 26.7(28.7) / 37.9(29.7)
Dose of clozapine, mg/day: 515.6(138.7) / 414.3(96.9)

**Interventions** **Intervention - group 1.:** Risperidone, up to 6mg/day, n=16

**Intervention - group 2.:** Placebo, n=14

**Notes about the interventions:**
All participants continued to receive the same dose of clozapine, with the same daily administration schedule.

All participants originally received 1 identical pill containing either 2mg risperidone or placebo. This was increased to 2 pills after the first week and to 3 pills after the second week. The dose would be adjusted downward after the 3rd week based on tolerability or signs of diminished efficacy compared with earlier weeks.

Biperiden (2-6mg/day) was added to treat EPS if needed

**Outcomes** **Global state & service outcomes (e.g. CGI):** Average score/change in global state CGI-S

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS (PANSS POS was primary outcome); CDS

**Mental state (e.g. BPRS, PANSS, BDI):** Clinically significant response in mental state - PANSS total - no. with >=20% improvement

**General and psychosocial functioning (e.g. SFS):** Average score/change in general functioning - GAF

**Adverse events:** Number of people with general adverse effects

**Adverse events:** Number of people with specific adverse effects - UKU side effect scale, paper reports % experiencing sleepiness/sedation and impaired memory

**Adverse events:** Average score/change in specific adverse effects - AIMS; BAS; SAS

**Quality of Life:** Average score/change in quality of life QLS

**Other:** Clinically significant weight change (>=7% change); QTc interval; clinical laboratory measures including serum prolactin levels; vital signs (BP and pulse)

**Quality** **1.1 The study addresses an appropriate and clearly focused question.:** Well covered

**1.2 The assignment of subjects to treatment groups is randomised.:** Adequately addressed

**1.3 An adequate concealment method is used.:** Well covered

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered

**1.5 The treatment and control groups are similar at the start of the trial.:** Well covered

**1.6 The only difference between groups is the treatment under investigation.:** Not addressed

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** <20%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Not reported adequately

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not addressed

**2.1 How well was the study done to minimise bias?: +**

**References of included studies (update)**

**CHANG2008**
Chang,J.S.; Ahn,Y.M.; Park,H.J.; Lee,K.Y.; Kim,S.H.; Kang,U.G.; Kim,Y.S. (2008) Aripiprazole augmentation in clozapine-treated patients with refractory schizophrenia: An 8-week, randomized, double-blind, placebo-controlled trial. *Journal of Clinical Psychiatry.* 69(**5**): 720-31.

**FREUDENREICH2007**
Freudenreich, O., Henderson, D.C., Walsh, J.P., Culhane, M.A., Goff, M.D. (2007) Risperidone augmentation for schizophrenia partially responsive to clozapine: A double-blind, placebo-controlled trial. *Schizophrenia Research.* 92: 90-94.

**HONER2006**
Honer,W.G.; Thornton,A.E.; Chen,E.Y.; Chan,R.C.; Wong,J.O.; Bergmann,A.; Falkai,P.; Pomarol,Clotet E.; McKenna,P.J.; Stip,E.; Williams,R.; MacEwan,G.W.; Wasan,K.; Procyshyn,R.; Clozapine-and-Risperidone-Enhancement (2006) Clozapine alone versus clozapine and risperidone with refractory schizophrenia. *The New England Journal of Medicine.* 354: 472 - 482.

**JOSIASSEN2005**
Josiassen,R.C.; Joseph,A.; Kohegyi,E.; Stokes,S.; Dadvand,M.; Paing,W.W.; Shaughnessy,R.A. (2005) Clozapine augmented with risperidone in the treatment of schizophrenia: a randomized, double-blind, placebo-controlled trial. *American Journal of Psychiatry.* 162(1): 130 - 136.

**SHILOH1997**
Shiloh R, Zemishlany Z, Aizenberg D, Radwan M, Schwartz B, Dorfman-Etrog P, Modai I, Khaikin M, Weizman A. (1997) Sulpiride augmentation in people with schizophrenia partially responsive to clozapine. A double-blind, placebo-controlled study. *British Journal of Psychiatry*. 171:569-73.

**YAGCIOGLU2005**

*Anil Yagcioglu, A.E.; Akdede,Berna B.K.; Turgut,Tolga I.; Tumuklu, M; Yazici, M.K.; Alptekin, K.; Ertugrul, A.; Jayathilake, K.; Gogus, A.; Tunca, Z.; Meltzer, H.Y. (2005) A double-blind controlled study of adjunctive treatment with risperidone in schizophrenic patients partially responsive to clozapine: efficacy and safety. *Journal of Clinical Psychiatry* 66(1): 63-72.

Akdede,B.B.; nil Yaciolu,A.E.; Alptekin,K.; Turgut,T.I.; Tumuklu,M.; Yazici,M.K.; Jayathilake,K.; Tunca,Z.; Gou,A.; Meltzer,H.Y. (2006) A double-blind study of combination of clozapine with risperidone in patients with schizophrenia: effects on cognition. *Journal of Clinical Psychiatry.* 67(12): 1912 - 1919.

# Side effects of antipsychotic medication – studies not included in any other analysis (See full guideline for complete list of included studies)

**Characteristics of included studies (update)**

| **Study ID** | **ATMACA2003** |
|---|---|
| **General info** | **Clinical Question:** Acute treatment: with antipsychotic medication<br>**Funding source:** None declared<br>**Published or unpublished data?:** Published |
| **Methods** | **Type of study:** Individual randomised trial<br>**Type of analysis:** Completer - Paper unclear about method of analysis<br>**Blindness:** Single-blind<br>**Duration:** No. weeks of treatment - *6*<br>**Raters:** Independent of treatment<br>**Design:** Single-centre - Firat University School of Medicine, Elazig, Turkey<br>**Number of people screened, excluded & reasons:** - 71 participants were screened, 9 were excluded from the analysis because of: Comorbid Axis I disorder (3); history of alcohol misuse (1) and physical reasons (5).<br>- Of the 62 participants who started treatment, 6 were excluded from the study due to requirement of additional drug, or discontinuation because of intolerance. These patients were not included in the analysis.<br>**Notes about study methods:** Randomisation procedure not reported |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 100%<br>**Diagnostic tool:** DSM-IV<br>**Inclusion criteria:** - DSM-IV diagnosis<br>- Free from all medications for >=2 weeks prior to randomisation.<br><br>The no treatment group comprised 11 patients suffering from a range of psychiatric disorders who received no psychopharmacologic treatment because of pregnancy (3), diagnostic purposes (3) or treatment with cognitive and behavioural psychotherapeutic approaches (5)<br>**Exclusion criteria:** - Presence of severe physical illness; history of lipid-lowering treatment, and presence of any endocrinologic disorder<br>- History of alcohol and substance misuse or dependence |

- Comorbid Axis I disorder

**Total sample size:** No. randomised - *62*

**Total sample size:** ITT population - Number used in the analysis: 56 (not ITT*)*

**Gender:** % female - 63%

**Age:** Mean - 30

**Ethnicity:** Not reported

**Setting:** Inpatient

**History:** [Quetiapine / Olanzapine / Risperidone / Clozapine / No treatment]
Mean duration of illness, yrs: 5.9(3.7) / 6.3(3.3) / 5.6(4.1) / 6.6(3.8) / not reported

**Baseline stats:** [Quetiapine / Olanzapine / Risperidone / Clozapine / No treatment]
PANSS: 94.93 / 93.53 / 94.41 / 94.61 / N/A

**Notes about participants:** [Quetiapine / Olanzapine / Risperidone / Clozapine / No treatment]
Never taken psychotropic drugs: 3 / 5 / 6 / 5 / N/A

All other participants had been treated with antipsychotics but had been off medication for 15 days to 1.5 years. In addition, they had received additional treatment with the following drugs: neuroleptics (4), depot neuroleptics (9), clozapine (4), olanzapine (3) and risperidone (1)

**Interventions**

**Intervention - group 1:** Quetiapine, Mean dose = 535.7(110.5) mg/d, n=14

**Intervention - group 2:** Olanzapine, mean dose = 15.7(4.8)mg/d, n=13

**Intervention - group 3:** Risperidone, mean dose = 6.7(3.6)mg/d, n=13

**Intervention - group 4:** Clozapine, mean dose = 207.1(62.4)mg/d, n=13

No treatment group, n=11

**Notes about the interventions:** All patients received a routine hospital diet

**Outcomes**

**Leaving the study early:** Leaving because of adverse effects

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Mental state:** Average score/change in mental state - PANSS

**Other:** BMI; Weight change; triglyceride and leptin levels

**Quality**

**1.1 The study addresses an appropriate and clearly focused question:** Adequately addressed

**assessment**

**1.2 The assignment of subjects to treatment groups is randomised:** Not reported adequately

**1.3 An adequate concealment method is used:** Not addressed

**1.4 Subjects and investigators are kept blind about treatment allocation:** Adequately addressed

**1.5 The treatment and control groups are similar at the start of the trial:** Adequately addressed

**1.6 The only difference between groups is the treatment under investigation:** Well covered

**1.7 All relevant outcomes are measured in a standard, valid and reliable way:** Adequately addressed

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** <20%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis):** <20%

**1.10 Where the study is carried out at more than one site, results are comparable for all sites:** Not applicable

**2.1 How well was the study done to minimise bias?:** +

| **Study ID** | **LIEBERMAN2003B** |
|---|---|
| **General info** | **Clinical Question:** Initial treatment: with antipsychotic medication |
| | **Comparison:** [Primary & sub-groups] Clozapine SGA vs. chlorpromazine - sub-groups: phase of illness = first-episode/early schizophrenia, duration of intervention = long-term (>52 weeks) |
| | **Funding source:** Pharmaceutical industry |
| | **Published or unpublished data?:** Published |
| **Methods** | **Type of study:** Individual randomised trial |
| | **Type of analysis:** ITT - All participants that started study medication. Kaplan-Meier estimates for missing data. |
| | **Type of analysis:** LOCF |
| | **Type of analysis:** Observed case |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment - 52 |
| | **Raters:** Not stated to be independent of treatment |
| | **Design:** Single-centre - Beijing, China |

| | |
|---|---|
| | **Number of people screened, excluded & reasons:** 2708 screened, 171 met criteria for first episode, 164 gave consent and randomised, 4 dropped out prior to start of treatment |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 76% |
| | **Diagnosis:** Other schizophrenia related [%] Schizophreniform 24% |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:** DSM-IV diagnosis of schizophrenia or schizophreniform disorder<br>- Duration of symptoms <=60 months<br>- No prior treatment with antipsychotics, or if treated, no more than 14 days over lifetime<br>- Aged 16-40<br>- Current psychotic symptoms of moderate severity or greater, as measured by the BPRS psychotic items |
| | **Total sample size:** ITT population - 160 |
| | **Total sample size:** No. randomised - 164 |
| | **Gender:** % female - 48% |
| | **Age:** Mean - 28.7 (6.9) |
| | **Age:** Range - 15-42 |
| | **Ethnicity:** 100% Chinese |
| | **Setting:** Outpatient |
| | **Setting:** Inpatient |
| | **History:** Age of onset of first psychotic symptom: 27.2 (6.5)<br>Duration of symptoms (months): 18.4 (17.8) |
| | **Baseline stats:** BPRS 43.8 (5.1)<br>CGI 5.6 (0.6)<br>GAF 35.8 (7.8) |
| **Interventions** | **Intervention - group 1:** Clozapine, max 400mg/day, n=80 |
| | **Intervention - group 2:** Chlorpromazine, max 600mg/day, n=80 |
| | **Notes about the interventions:** Both groups received benztropine. Antipsychotic dose was titrated during the first 28 days depending on clinical response and adverse events. Patients received inpatient care for 12 weeks then followed as outpatients for 9 months. |
| **Outcomes** | **Leaving the study early:** Leaving because of adverse effects - data added to RevMan |
| | **Leaving the study early:** Leaving due to any reason (non-adherence to study protocol) - data added to RevMan |
| | **Global state & service outcomes:** Clinically significant response in global state. Remission defined as 50% decrease in BPRS total, with no score >3 on any psychosis item, and a CGI-severity item of <=3 - data added to RevMan |

| | |
|---|---|
| | **Global state & service outcomes:** Average score/change in global state. Time to remission, CGI - data added to RevMan |
| | **Mental state:** Average score/change in mental state. BPRS Chinese, SANS Chinese - data added to RevMan |
| | **General and psychosocial functioning:** Average score/change in general functioning - GAF - data added to RevMan |
| | **Adverse events:** Number of people with specific adverse effects - Various - data added to RevMan |
| | **Adverse events:** Average score/change in specific adverse effects - SAS - data added to RevMan |
| | **Other:** Laboratory parameters: neutrophils, lymphocytes, white blood cells, glucose, EKG heart rate, EKG QT interval; body weight - data added to RevMan |
| **Quality assessment** | **1.1 The study addresses an appropriate and clearly focused question:** Well covered |
| | **1.2 The assignment of subjects to treatment groups is randomised:** Not reported adequately |
| | **1.3 An adequate concealment method is used:** Not addressed |
| | **1.4 Subjects and investigators are kept blind about treatment allocation:** Adequately addressed |
| | **1.5 The treatment and control groups are similar at the start of the trial:** Well covered |
| | **1.6 The only difference between groups is the treatment under investigation:** Adequately addressed |
| | **1.7 All relevant outcomes are measured in a standard, valid and reliable way:** Well covered |
| | **1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** <20% |
| | **1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis):** <20% |
| | **1.10 Where the study is carried out at more than one site, results are comparable for all sites:** Not applicable |
| | **2.1 How well was the study done to minimise bias?:** + |
| **Exclusion status** | **Reason for exclusion:** Not a relevant comparison |

| | |
|---|---|
| **Study ID** | **MCQUADE2004** |
| **General info** | **Funding source:** Pharmaceutical industry |
| | **Published or unpublished data?:** Published |
| **Methods** | **Type of study:** Individual randomised trial |

**Type of analysis:** Observed case

**Type of analysis:** LOCF - LOFC data set excluded those who did not receive at least 14 days of study medication or who did not have a baseline or an on-treatment weight measurement.

**Type of analysis:** ITT - all those assigned to treatment who received study medication and who had a baseline and on-treatment measure.

**Blindness:** Double-blind

**Duration:** No. weeks of treatment - 26

**Raters:** Not stated to be independent of treatment

**Design:** Multi-centre - 56 sites in the US (n=41), Canada (n=5), Argentina (n=4), Brazil (n=3) and Mexico (N=3)

**Number of people screened, excluded & reasons:** screened: n=378; excluded: n=61
Reasons for exclusion not explicitly stated.

**Notes about study methods:** Randomisation procedure not reported

**Participants**

**Diagnosis:** Schizophrenia [% of sample] 100

**Diagnostic tool:** DSM-IV

**Inclusion criteria:** Aged 18+ with an acute relapse requiring hospitalisation.

- previous response to a neuroleptic medication other than clozapine and if treated as an outpatient for at least 1 continuous 3-month period during the past 12 months.
- women of childbearing age with a negative pregnancy test and using an acceptable form of contraception.
-PANSS >=60; and a score of >=4 on at least 2 of the following: delusions, hallucinatory behaviour, conceptual disorganisation, or suspiciousness

**Exclusion criteria:** Schizoaffective disorder or substance use disorder; positive screen for cocaine or blood alcohol concentration => 0.08%; a clinical history of delirium, dementia, amnesia, or bipolar disorder.
- patients hospitalised for >=14 days prior to screening
- patients deemed refractory to neuroleptic medication; failure to respond to olanzapine; likely to require concomitant therapy.
- Pregnant or nursing women
-Known allergy to aripiprazole, quinolinones, or olanzapine; suicidal ideation or suicide attempts; likely requirement for medications that might interfere with analysis of study drugs.
- participation in previous aripiprazole study; use of investigational drug within 4 weeks of randomisation
- clinically significant abnormal laboratory results at screening.

**Total sample size:** No. randomised - 317

**Total sample size:** ITT population - 309

**Gender:** % female - 28%

**Age:** Mean - 38.4

**Setting:** Inpatient

**History:** [Olanzapine / Aripiprazole]
Schizophrenia type: N(%)
Disorganised: 10(6) / 7(4)
Catatonic: 0(0) / 0(0)
Paranoid: 138(86) / 133(85)
Residual: 0(0) / 3(2)
Undifferentiated: 13(8) / 13(8)

Mean age at time of first hospitalisation: 24.15 / 24.86

**Baseline stats:** [Olanzapine / Aripiprazole]
Mean weight kg: 81.7 / 81.3
Mean BMI: 27.7 / 27.6

**Interventions**

**Intervention - group 1:** Olanzapine, 10-20 mg/day; n=161

**Intervention - group 2:** Aripiprazole, 15-30 mg/day; n=156

**Notes about the interventions:** Minimum 2-day washout period of any neuroleptic medication or 1 depot cycle after the most recent depot antipsychotic injection.

Olanzapine:
starting dose = 10mg/day. Doses could be increased weekly during the first 2 weeks based on CGI-I score. Dose range = 10-20mg/day
- mean dose = 16.5mg/day

Aripiprazole:
- starting dose = 15mg/day. Doses could be increased weekly during the first 2 weeks based on CGI-I score. Dose range = 15-30mg/day
- mean dose = 25.1mg/day

- Most psychotropic medications not permitted. Anticholinergic treatment of EPS not permitted at screening but could be administered in the study at a dose equivalent to <=6mg/day of benztropine. No anticholinergic treatment could be administered within 12 hours of assessment. Lorazepam <=4 mg/day permitted but could not be administered within 4 hours of assessment.

**Outcomes**

**Death:** Suicide possibly suicide or homicide reported

**Leaving the study early:** Leaving because of adverse effects

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol) data added to RevMan - only leaving study early

| | |
|---|---|
| | entered due to high drop out<br>**Global state & service outcomes:** Average score/change in global state<br>**Global state & service outcomes:** Clinically significant response in global state - CGI- % response defined as CGI-I score of 1 or 2 (very much improved or much improved)<br>**Mental state:** Average score/change in mental state - PANSS<br>**Adverse events:** Number of people with specific adverse effects<br>**Adverse events:** Number of people with general adverse effects<br>**Other:** - average change in BMI and body weight<br><br>- Clinically significant BMI change defined as a change >=7%<br><br>-QTC intervals; serum lipids; blood pressure; heart rate; serum glucose levels; prolactin levels |
| **Quality assessment** | **1.1 The study addresses an appropriate and clearly focused question:** Well covered<br><br>**1.2 The assignment of subjects to treatment groups is randomised:** Not reported adequately<br>**1.3 An adequate concealment method is used:** Not addressed<br>**1.4 Subjects and investigators are kept blind about treatment allocation:** Well covered<br>**1.5 The treatment and control groups are similar at the start of the trial:** Adequately addressed<br>**1.6 The only difference between groups is the treatment under investigation:** Not addressed<br>**1.7 All relevant outcomes are measured in a standard, valid and reliable way:** Well covered<br>**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** >50% 72%<br>**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis):** >50% 72%<br>**1.10 Where the study is carried out at more than one site, results are comparable for all sites:** Not addressed<br>**2.1 How well was the study done to minimise bias?:** + |

| **Study ID** | **MELTZER2003** |
|---|---|
| **General info** | **Funding source:** Pharmaceutical industry |

| | |
|---|---|
| | **Published or unpublished data?:** Published |
| **Methods** | **Type of study:** Individual randomised trial (effectiveness/pragmatic) |
| | **Type of analysis:** ITT - All randomised participants |
| | **Blindness:** Only raters blind |
| | **Duration:** No. weeks of treatment - 104 |
| | **Raters:** Independent of treatment |
| | **Design:** Multi-centre - 67 centres in 11 countries (US, Canada, France, Italy, UK, Czech Republic, Hungary, Croatia, South Africa, Argentina and Chile) |
| | **Number of people screened, excluded & reasons:** 1065 screened, 980 eligible and gave consent, of which 24 never received study treatment for administrative reasons |
| | **Notes about study methods:** Randomisation blocked by country and medical centre<br>Allocation concealment not mentioned |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] - 62% |
| | **Diagnosis:** Other schizophrenia related [%] - Schizoaffective 38% |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:** - Aged 18-65<br>- DSM-IV schizophrenia or schizoaffective disorder<br>- At high risk of suicide, defined as any of the following:<br>1) History of previous attempts or hospitalisations to prevent a suicide attempt in past 3 years<br>2) moderate or severe suicidal ideation with depressive symptoms<br>3) command hallucinations for self-harm within 1 week of enrolment. |
| | **Total sample size:** Safety population - 956 |
| | **Total sample size:** ITT population - 980 |
| | **Total sample size:** No. randomised - 980 |
| | **Gender:** % female - 39% |
| | **Age:** Mean - 37.1 (10.3) |
| | **Ethnicity:** White 71%<br>Black 15%<br>Oriental 1%<br>Other 13% |
| | **Setting:** Inpatient |

**Setting:** Outpatient

**History:** 84% had ever been hospitalised to prevent a suicide attempt

**Baseline stats:** [Clozapine / Olanzapine]
Ever attempted suicide: 84% / 82%
No of lifetime suicide attempts: 3.6 (7.5) / 3.5 (4.5)
Attempted suicide in past 36 months: 63% / 64%

**Interventions**

**Intervention - group 1:** Olanzapine, mean 16.6 (6.4) mg; n=490

**Intervention - group 2:** Clozapine, mean 274.2 (155.0) mg; n=490

**Notes about the interventions:** To ensure safety of participants, clinicians were allowed to make any necessary interventions to prevent occurrence of suicide attempts, including changing doses, medications, and increasing surveillance.

**Outcomes**

**Death:** Suicide

**Death:** Natural causes

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Leaving the study early:** Leaving because of adverse effects

**Global state & service outcomes:** Re-hospitalisation - Hospitalisation due to imminent suicide risk

**Behaviour:** Clinically significant response in behaviour - Various measures of suicidality (attempts, ideation)

**Behaviour:** Average score/change in behaviour - CGI-SS

**Engagement with services:** Clinically important engagement with services - Number receiving rescue interventions for suicide attempts (including hospitalisation, addition or change of medication, psychotherapy, crisis team, ECT)

**Adverse events:** Number of people with specific adverse effects Various

**Other:** Medication compliance

**Quality assessment**

**1.1 The study addresses an appropriate and clearly focused question:** Well covered

**1.2 The assignment of subjects to treatment groups is randomised:** Adequately addressed

**1.3 An adequate concealment method is used:** Not addressed

**1.4 Subjects and investigators are kept blind about treatment allocation:** Poorly addressed

**1.5 The treatment and control groups are similar at the start of the trial:** Well covered

**1.6 The only difference between groups is the treatment under investigation:** Poorly addressed

**1.7 All relevant outcomes are measured in a standard, valid and reliable way:** Well covered

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was**

**completed?:** 20-50%

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis):** 20-50%

**1.10 Where the study is carried out at more than one site, results are comparable for all sites:** Not addressed

**2.1 How well was the study done to minimise bias?:** +

**References of included studies (update)**

**ATMACA2003**

Atmaca,M.; Kuloglu,M.; Tezcan,E.; Ustundag,B. (2003) Serum leptin and triglyceride levels in patients on treatment with atypical antipsychotics. *Journal of Clinical Psychiatry.* 64(**5**), 598-604.

Keefe,R.S.; Young,C.A.; Rock,S.L.; Purdon,S.E.; Gold,J.M.; Breier,A.; HGGN-Study-Group (2006) One-year double-blind study of the neurocognitive efficacy of olanzapine, risperidone, and haloperidol in schizophrenia. *Schizophrenia Research.* 81: 1 - 15.

**LIEBERMAN2003B**

Lieberman,J.A.; Phillips,M.; Gu,H.; Stroup,S.; Zhang,P.; Kong,L.; Ji,Z.; Koch,G.; Hamer,R.M. (2003) Atypical and conventional antipsychotic drugs in treatment-naive first-episode schizophrenia: a 52-week randomized trial of clozapine vs chlorpromazine. *Neuropsychopharmacology,* 28: 995 - 1003.

**MCQUADE2004**

McQuade,R.D.; Stock,E.; Marcus,R.; Jody,D.; Gharbia,N.A.; Vanveggel,S.; Archibald,D.; Carson,W.H. (2004) A comparison of weight change during treatment with olanzapine or aripiprazole: results from a randomized, double-blind study. *Journal of Clinical Psychiatry.* 65 Suppl 18: 47 - 56.

**MELTZER2003**

Meltzer,H.Y.; Alphs,L.; Green,A.I.; Altamura,A.C.; Anand,R.; Bertoldi,A.; Bourgeois,M.; Chouinard,G.; Islam,M.Z.; Kane,J.; Krishnan,R.; Lindenmayer,J.P.; Potkin,S.; International-Suicide-Prevention-Trial-Study-Group (2003) Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Archives of General Psychiatry.* 60: 82 - 91.

Glick,I.D.; Zaninelli,R.; Hsu,C.; Young,F.K.; Weiss,L.; Gunay,I.; Kumar,V. (2004) Patterns of concomitant psychotropic medication use during a 2-year study comparing clozapine and olanzapine for the prevention of suicidal behavior. *Journal of Clinical Psychiatry.* 65(**5**): 679 - 685.

Potkin,S.G.; Alphs,L.; Hsu,C.; Krishnan,K.R.; Anand,R.; Young,F.K.; Meltzer,H.; Green,A.; InterSePT Study Group (2003) Predicting suicidal risk in schizophrenic and schizoaffective patients in a prospective two-year trial. *Biological Psychiatry.* 54(**4**): 444 - 452.

## Effectiveness of antipsychotic medication

### Characteristics of included studies (update)

| Study ID | CATIE |
|---|---|
| General info | **Funding source:** Non-industry support |
| | **Published or unpublished data?:** Published |
| Method | **Type of study:** Individual randomised trial (effectiveness/pragmatic) |
| | **Type of analysis:** ITT - Randomized patients who received at least one dose of study medication |
| | **Blindness:** Double-blind |
| | **Duration:** No. weeks of treatment - 78 |
| | **Raters:** Not stated to be independent of treatment |
| | **Design:** Multi-centre - 57 clinical sites, US |
| | **Number of people screened, excluded & reasons:** 1894 people screened, 401 excluded due to the following (N): Did not meet study criteria (124), Declined (109), Decided against changing antipsychotic agent (33), other reasons (135). A further 33 participants from one site were excluded from the analysis due to concerns regarding the integrity of the data. |
| | **Notes about study methods:** Randomisation procedures not reported in the current paper details in secondary paper which described method in more detail. |
| Participants | **Diagnosis:** Schizophrenia [% of sample] 100% |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:**<br>- Aged 18 to 65 years of age;<br>- Primary diagnosis of schizophrenia<br>- Able to take oral antipsychotic medication |
| | **Exclusion criteria:**<br>- Diagnosis of schizoaffective disorder, mental retardation, or other cognitive disorders;<br>- history of serious AEs to the proposed treatments;<br>- had had only one schizophrenic episode;<br>- history of treatment resistance (defined by persistence of severe symptoms despite adequate trials of one of the proposed treatments or prior to clozapine) |

- pregnant or breastfeeding;
- serious and unstable medical condition

**Total sample size:** ITT population 1432

**Total sample size:** No. randomised 1493

**Gender:** % female 26

**Age:** Mean 41

**Ethnicity:** White - 60%
Black - 35%
Other - 5%

Spanish, Hispanic, or Latino ethnicity - 12%

**Setting:** Inpatient

**Setting:** Outpatient

**History:** Age at first treatment for any behavioural or emotional problem - 24
Years since first antipsychotic medication - 14.4

**Baseline stats:** PANSS total - 75.7(17.6)

**Notes about participants:**
Diagnoses at baseline, n (%) of whole sample:
Depression 405(28)
Alcohol dependence or alcohol misuse 358(25)
Drug dependence or drug misuse 422(29)
Obsessive–compulsive disorder 73(5)
Other anxiety disorder 4199(14)

**Interventions** **Intervention - group 1.:** Olanzapine; N = 336

**Intervention - group 2.:** Perphenazine; N = 261**
Patients with tardive dyskinesia were not assigned to perphenazine.

**Intervention - group 3.:** quetiapine; N = 337

**Intervention - group 4.:** Risperidone; N = 341
**Intervention – group 5**: ziprasidone ; N = 185 ***

**Notes about the interventions:**
Study medication consisted of identical-appearing capsules contained olanzapine (7.5 mg), quetiapine (200 mg), risperidone (1.5 mg), perphenazine (8 mg), or (after January 2002) ziprasidone (40 mg).
- Dose of medications was flexible, ranging from 1-4 capsules per day based on clinical judgement,
- Overlap of the antipsychotics received before study entry permitted up until 4 weeks to allow gradual titration of the study medication
- Apart from additional antipsychotics, concomitant medications were permitted throughout
- To minimise initial side effects, patients assigned to quetiapine received one 100-mg capsule on days 1 and 2, one twice daily on day 3, and one for the first dose of day 4.

Phase 1 continued for 18 months or until discontinuation of study drug. Patients whose assigned treatment was discontinued could receive other treatments in phases 2 and 3.

**Patients with tardive dyskinesia were excluded from the perphenazine group.
***Ziprasidone was added to the study after approximately 40 percent of patients had been enrolled.

**Outcomes**

**Leaving the study early:** Leaving due to any reason (non-adherence to study protocol)

**Leaving the study early:** Leaving because of adverse effects

**Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS

**Adverse events:** Number of people with general adverse effects

**Adverse events:** Average score/change in specific adverse effects - BAS; AIMS; SAS

**Adverse events:** Number of people with specific adverse effects

**Other:** Rate of discontinuation; Weight, BMI, changes in baseline metabolic values; concomitant medication use

**Quality**

**1.1 The study addresses an appropriate and clearly focused question.:** Well covered

**1.2 The assignment of subjects to treatment groups is randomised.:** Adequately addressed

**1.3 An adequate concealment method is used.:** Not reported adequately

**1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Well covered

**1.5 The treatment and control groups are similar at the start of the trial.:** Adequately addressed

**1.6 The only difference between groups is the treatment under investigation.:** Not addressed

**1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered

**1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** >50% Primary outcome of phase 1 was rate and time until discontinuation of medication

**1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis).**
**:** Well covered

**1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not reported adequately

**2.1 How well was the study done to minimise bias?:** +

| **Study ID** | **CUtLASS** |
|---|---|
| **General info** | **Funding source:** Non-industry support |
| | **Published or unpublished data?:** Published |
| **Method** | **Type of study:** Individual randomised trial (effectiveness/pragmatic) |
| | **Type of study:** Economic evaluation |
| | **Type of analysis:** ITT - Missing data assumed ignorable or random |
| | **Blindness:** Only raters blind |
| | **Duration:** No. weeks of treatment 52 |
| | **Raters:** Independent of treatment |
| | **Design:** Multi-centre - 5 medical schools covering 14 NHS trusts in UK |
| | **Notes about study methods:** Randomisation via remote telephone service. After stratifying by centre, allocation was done using randomised permuted blocks within strata. |
| **Participants** | **Diagnosis:** Schizophrenia [% of sample] 75% |
| | **Diagnosis:** Other schizophrenia related [%] Schizophreniform 4%<br>Schizoaffective 17%<br>Delusional disorder 4% |
| | **Diagnostic tool:** DSM-IV |
| | **Inclusion criteria:**<br>- DSM-IV schizophrenia, schizoaffective disorder, or delusional disorder<br>- Age 18-65<br>- At least 1 month since the first onset of positive psychotic symptoms<br>- Psychiatrist electing to change the current FGA or SGA treatment because of inadequate clinical response or intolerance. |
| | **Exclusion criteria:**<br>- Substance misuse or a medical disorder considered clinically to be the major cause of positive psychotic symptoms<br>- History of neuroleptic malignant syndrome. |
| | **Total sample size:** No. randomised 227 |

**Total sample size:** ITT population 227

**Gender:** % female 32%

**Age:** Mean 41

**Ethnicity:** 75%

**Setting:** Outpatient

**Setting:** Inpatient

**History:**
[FGA / SGA]
First episode: 13% / 10%

Antipsychotic use before randomisation
FGAs: 92% / 91%
Depots: 40% / 34%
SGAs: 21% / 17%
None: 2% / 2%
Antipsychotic polypharmacy: 11% / 14%

**Baseline stats:**
[FGA / SGA]
PANSS: 72.9 (17.2) / 71.3 (16.5)
GAF: 45.6 (14.9) / 42.7 (13.6)
CDS: 6.6 (5.0) / 6.9 (5.2)

**Interventions** **Intervention - group 1.:** FGAs; n=118

**Intervention - group 2.:** SGAs; n=109

**Notes about the interventions:**
FGA
Chlorpromazine hydrochloride, flupenthixol, haloperidol, loxapine, methotrimeprazine, sulpiride, trifluoperazine hydrochloride, zuclopenthixol, depot fluphenazine decanoate, flupenthixol decanoate, haloperidol decanoate, pipothiazine decanoate, zuclopenthixol decanoate. Thioridazine hydrochloride and droperidol were initially included by were withdrawn from licensed use during trial.

SGA
Risperidone, olanzapine, amisulpride, zotepinem and quetiapine fumarate.

The responsible psychiatrist chose the individual drug in each class prior to randomisation. Numbers prescribed with each drug were

| | |
|---|---|
| | reported. |
| **Outcomes** | **Death:** Natural causes |
| | **Leaving the study early:** Leaving due to any reason (non-adherence to study protocol) |
| | **Global state & service outcomes (e.g. CGI):** Re-hospitalisation |
| | **Mental state (e.g. BPRS, PANSS, BDI):** Average score/change in mental state - PANSS, CDS |
| | **General and psychosocial functioning (e.g. SFS):** Average score/change in general functioning - GAF |
| | **Adverse events:** Average score/change in specific adverse effects - SAS, BAS, AIMS |
| | **Adverse events:** Average score/change in general adverse effects – ANNSERS (Antipsychotic Non-Neurological Side-Effects Rating Scale) |
| | **Satisfaction with treatment:** Service user satisfaction - Drug Attitude Inventory |
| | **Quality of Life:** Average score/change in quality of life - QLS |
| | **Other:** Compliance scale, polypharmacy |
| **Quality** | **1.1 The study addresses an appropriate and clearly focused question.:** Well covered |
| | **1.2 The assignment of subjects to treatment groups is randomised.:** Well covered |
| | **1.3 An adequate concealment method is used.:** Well covered |
| | **1.4 Subjects and investigators are kept 'blind' about treatment allocation.:** Adequately addressed |
| | **1.5 The treatment and control groups are similar at the start of the trial.:** Adequately addressed |
| | **1.6 The only difference between groups is the treatment under investigation.:** Poorly addressed |
| | **1.7 All relevant outcomes are measured in a standard, valid and reliable way.:** Well covered |
| | **1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?:** <20% |
| | **1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). :** Well covered |
| | **1.10 Where the study is carried out at more than one site, results are comparable for all sites.:** Not reported adequately |
| | **2.1 How well was the study done to minimise bias?:** + |

**References of included studies (update)**

**CATIE**

Campbell,D.B.; Ebert,P.J.; Skelly,T.; Stroup,T.S.; Lieberman,J.; Levitt,P.; Sullivan,P.F. (2008) Ethnic stratification of the association of RGS4 variants with antipsychotic treatment response in schizophrenia. *Biological Psychiatry.* 63(**1**), 32-41.

Davis,S.M.; Koch,G.G.; Davis,C.E.; LaVange,L.M. (2003) Statistical Approaches to Effectiveness Measurement and Outcome-Driven Re-Randomizations in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Studies. *Schizophrenia Bulletin* 29(**1**): 73-80.

DeLisi,L.E.; Nasrallah,H.A. (2005) The CATIE schizophrenia effectiveness trial. *Schizophrenia Research.*80(**1**): v-vi.

Goff,D.C.; Sullivan,L.M.; McEvoy,J.P.; Meyer,J.M.; Nasrallah,H.A.; Daumit,G.L.; Lamberti,S.; D'Agostino,R.B.; Stroup,T.S.; Davis,S.; Lieberman,J.A. (2005) A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. *Schizophrenia Research.* 80(**1**): 45 - 53.

Heinrichs,R.Walter (2007) Cognitive improvement in response to antipsychotic drugs: Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE trial. *Archives of General Psychiatry* 64(**6**): 632.

Keefe,R.S.; Bilder,R.M.; Davis,S.M.; Harvey,P.D.; Palmer,B.W.; Gold,J.M.; Meltzer,H.Y.; Green,M.F.; Capuano,G.; Stroup,T.S.; McEvoy,J.P.; Swartz,M.S.; Rosenheck,R.A.; Perkins,D.O.; Davis,C.E.; Hsiao,J.K.; Lieberman,J.A.; CATIE,Investigators; Neurocognitiv (2007) Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. *Archives of General Psychiatry* 64: 633 - 647.

Keefe,R.S.; Mohs,R.C.; Bilder,R.M.; Harvey,P.D.; Green,M.F.; Meltzer,H.Y.; Gold,J.M.; Sano,M. (2003) Neurocognitive Assessment in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Project Schizophrenia Trial: Development, Methodology, and Rationale. *Schizophrenia Bulletin* 29(**1**); 45-55.

Lieberman,J.A.; Stroup,T.S.; McEvoy,J.P.; Swartz,M.S.; Rosenheck,R.A.; Perkins,D.O.; Keefe,R.S.; Davis,S.M.; Davis,C.E.; Lebowitz,B.D.; Severe,J.; Hsiao,J.K.; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators (2005) Effectiveness of antipsychotic drugs in patients with chronic schizophrenia.. *New England Journal of Medicine.* 353(**12**): 1209 - 1223.

McEvoy,J.P. (2006/07) An overview of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study. *CNS Spectrums.* 11(Suppl 7): 4 - 8.

McEvoy,J.P.; Lieberman,J.A.; Stroup,T.S.; Davis,S.M.; Meltzer,H.Y.; Rosenheck,R.A.; Swartz,M.S.; Perkins,D.O.; Keefe,R.S.; Davis,C.E.; Severe,J.; Hsiao,J.K.; CATIE,Investigators (2006) Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *American Journal of Psychiatry.* 163(**4**): 600 - 610.

Meyer,J.M.; Davis,V.G.; Goff,D.C.; McEvoy,J.P.; Nasrallah,H.A.; Davis,S.M.; Rosenheck,R.A.; Daumit,G.L.; Hsiao,J.; Swartz,M.S.; Stroup,T.S.; Lieberman,J.A. (2008) Change in metabolic syndrome parameters with antipsychotic treatment in the CATIE Schizophrenia Trial: Prospective data from phase 1.*Schizophrenia Research.* 101(**1-3**):

Nasrallah,H.A. (2006/07) Metabolic findings from the CATIE trial and their relation to tolerability. *CNS Spectrums.* 11(Suppl 7): 32 - 39.

Nasrallah,H.A. (2007) The roles of efficacy, safety, and tolerability in antipsychotic effectiveness: practical implications of the CATIE schizophrenia trial. *Journal of Clinical Psychiatry.* 68 Suppl 1: 5 - 11.

Rosenheck,R.; Swartz,M.; McEvoy,J.; Stroup,T.S.; Davis,S.; Keefe,R.S.E.; Hsiao,J.; Lieberman,J. (2007) Second-generation antipsychotics: Reviewing the cost-effectiveness component of the CATIE trial. *Expert Review of Pharmacoeconomics & Outcomes Research.* 7(**2**): 103-112.

Rosenheck,R.A.; Lieberman,J.A. (2007/02) Cost-effectiveness measures, methods, and policy implications from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) for schizophrenia. *Journal of Clinical Psychiatry.* 68(**2**): e05.

Stroup,T.S.; Lieberman,J.A.; McEvoy,J.P.; Swartz,M.S.; Davis,S.M.; Rosenheck,R.A.; Perkins,D.O.; Keefe,R.S.; Davis,C.E.; Severe,J.; Hsiao,J.K.; CATIE,Investigators (2006) Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. *The American Journal of Psychiatry.* 163: 611 - 622.

Stroup,T.S.; McEvoy,J.P.; Swartz,M.S.; Byerly,M.J.; Glick,I.D.; Canive,J.M.; McGee,M.F.; Simpson,G.M.; Stevens,M.C.; Lieberman,J.A. (2003) The National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project: schizophrenia trial design and protocol development. *Schizophrenia Bulletin.* 29(**1**): 15 - 31.

Stroup,T.Scott; Appelbaum,PaulS (200614/) Evaluation of "subject advocate" procedures in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia study. *Schizophrenia Bulletin* 32(**1**): 152.

Swartz,M.S.; Perkins,D.O.; Stroup,T.S.; Davis,S.M.; Capuano,G.; Rosenheck,R.A.; Reimherr,F.; McGee,M.F.; Keefe,R.S.; McEvoy,J.P.; Hsiao,J.K.; Lieberman,J.A.; CATIE Investigators (2007) Effects of antipsychotic medications on psychosocial functioning in patients with chronic schizophrenia: findings from the NIMH CATIE study. *American Journal of Psychiatry* 164: 428 - 436.

Swartz,M.S.; Perkins,D.O.; Stroup,T.S.; McEvoy,J.P.; Nieri,J.M.; Haak,D.C. (2003) Assessing clinical and functional outcomes in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial. *Schizophrenia Bulletin.* 29(**1**): 33 - 43.

**CUtLASS**

Davies,L.M.; Lewis,S.; Jones,P.B.; Barnes,T.R.; Gaughran,F.; Hayhurst,K.; Markwick,A.; Lloyd,H.; CUtLASS team (2007) Cost-effectiveness of first- v. second-generation antipsychotic drugs: results from a randomised controlled trial in schizophrenia responding poorly to previous therapy. *British Journal of Psychiatry, 191, 14-22.*

Jones,P.B.; Barnes,T.R.; Davies,L.; Dunn,G.; Lloyd,H.; Hayhurst,K.P.; Murray,R.M.; Markwick,A.; Lewis,S.W. (2006) Randomized controlled trial of the effect on Quality of Life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). *Archives of General Psychiatry.* 63(**10**): 1079 - 1087.

Lewis,S.W.; Davies,L.; Jones,P.B.; Barnes,T.R.; Murray,R.M.; Kerwin,R.; Taylor,D.; Hayhurst,K.P.; Markwick,A.; Lloyd,H.; Dunn,G. (2006) Randomised controlled trials of conventional antipsychotic versus new atypical drugs, and new atypical drugs versus clozapine, in people with schizophrenia responding poorly to, or intolerant of, current drug treatment. *Health Technology Assessment*, Volume 10, No. 17.

## Characteristics of excluded studies (update)

**ARNOULD2002**

**Reason for exclusion:** Conference abstract

**ARRANZ2007**

**Reason for exclusion:** Study not relevant

**ASCHERSVANUM2005[TOLLEFSON1997]**

**Reason for exclusion:** - Post hoc comparisons of gender differences. Original study was not designed to address this issue.

**ASSION2008**

**Reason for exclusion:** N<10 in each arm

**BELLACK2004**

**Reason for exclusion:** - Poor quality
- High attrition rate (>50% due to problems with assessors)
- Missing data particularly from the most severe patients
- Large group differences

**BENDER2006[NABER2005B]**

**Reason for exclusion:** - Dosing issues

**BOGGS2008**

**Reason for exclusion:** Open label

**BOULAY2007**

**Reason for exclusion:** - Inclusion criteria: patient and psychiatrist had decided to switch/ discontinue current medication

**BUCHANAN2007**

**Reason for exclusion:** Non AP augmentation

**BYERLY2008**

**Reason for exclusion:** Switching study

**CHAPLIN2007**

**Reason for exclusion:** Commentary on Potkin et al. (2006). A double-blind comparison of the atypical antipsychotics, risperidone and quetiapine, and placebo in patients with schizophrenia experiencing an acute exacerbation requiring hospitalisation. *Schizophrenia Research*, 85

**CHAWLA(2008)**

**Reason for exclusion:** Open label

**CHIAIE2007**

**Reason for exclusion:** Open Label

**CIUDAD2006**

**Reason for exclusion:** Open label

**CIUDAD2008**

**Reason for exclusion:** Observational study

**CORTESE2008**

**Reason for exclusion:** N<10 in one comparison arm

**CRESPOFACORRO2006A**

**Reason for exclusion:** Not relevant
Open label

**CRESPOFACORRO2006B**

**Reason for exclusion:** Open-label

**CRESPOFACORRO2007**

**Reason for exclusion:** Non RCT - Cohort study

**DANIEL2007**

**Reason for exclusion:** Primary paper excluded: not relevant

**DEHAAN2002**

**Reason for exclusion:** No relevant outcomes - looks at OCD symptoms only

**DEHAAN2003**

**Reason for exclusion:** N <10 in one comparison arm

**DELEON2003**

**Reason for exclusion:** Secondary analysis, lack of comparator

**DELEON2004**

**Reason for exclusion:** Lack of comparator

**DELEON2007**

**Reason for exclusion:** Lack of comparator

**DELIMA2005**

**Reason for exclusion:** Open label naturalistic study

**EDWARDS2003**

**Reason for exclusion:** Conference abstract

**FARIES2008**

**Reason for exclusion:** Open label and switching study

**FELDMAN2003[TRAN1997]**

**Reason for exclusion:** - Post-hoc analysis

**FRIEDMAN2008**

**Reason for exclusion:** Augmentation with non AP

**GALLHOFER2007**

**Reason for exclusion:** N <10 in each arm

**GANESAN2008**

**Reason for exclusion:** Open label

**GENC2007**

**Reason for exclusion:** No clozapine and placebo arm: (CLZ + AMI vs. CLZ + QUE)

**GHARABAWI2006[POTKIN2006]**

**Reason for exclusion:** Primary paper excluded

**GHARABAWI2007**

**Reason for exclusion:** Post-hoc analysis

**GOFF2008**

**Reason for exclusion:** Augmentation with non AP

**GOLDEN2008**

**Reason for exclusion:** Open-label

**GOLDSTEIN2002**

**Reason for exclusion:** Study was not originally designed to test for sex differences.

**GUZ2002**

**Reason for exclusion:** Paper not in English

**HABIL2007**

**Reason for exclusion:** - Open-label

**HARO2005**

**Reason for exclusion:** Cohort study (Non-RCT)

**HARO2007[HARO2005]**

**Reason for exclusion:** Cohort study (Non-RCT)

**HARVEY2003A**

**Reason for exclusion:** Not acute or promoting recovery

**HASHIMOTO2006B**

**Reason for exclusion:** Letter to editor

**HERTLING2003B**

**Reason for exclusion:** Paper not in English

**HIRSCH2002[Hirsch 1999]**

**Reason for exclusion:** Not an appropriate comparison (ziprasidone vs. haloperidol)

**HUANG2007**

**Reason for exclusion:** Observational cross-over study

**JESTE2003**

**Reason for exclusion:** - Population: >60years

**KAHN2007**

**Reason for exclusion:** Drug not licensed in the UK

**KAHN2008**

**Reason for exclusion:** Open-label

**KEEFE2003**

**Reason for exclusion:** After exclusions, total n across all 4 treatment groups = 16.

**KELLY2003**

**Reason for exclusion:** n<10 in each treatment arm in the cross-over study (total pop n=13)

**KENNEDY2003[TOLLESFSON1997]**

**Reason for exclusion:** - Post-hoc analysis >60s

**KILIAN2004**

**Reason for exclusion:** Paper not in English

**KINON2004A**

**Reason for exclusion:** - Switching study

**KINON2004B**

**Reason for exclusion:** No appropriate control group

**KINON2004C**

**Reason for exclusion:** - Rapid tranquilisation study

**KLUGE2007**

**Reason for exclusion:** Participants were not treatment resistant

**KRAKOWSKI2006**

**Reason for exclusion:** Study designed to look at the treatment of violent behaviour among hospitalised patients who physically assaulted others.

**KRIVOY2008**

**Reason for exclusion:** Augmentation with non AP

**LANE2008**

**Reason for exclusion:** Augmentation for non-AP

**LASSER2002**

**Reason for exclusion:** Open-label

**LASSER2004**

**Reason for exclusion:** No relevant comparison

**LAURIELLO2008**

**Reason for exclusion:** Outside scope

**LIEBERMAN2003**

**Reason for exclusion:** Not a relevant comparison

**LINDENMAYER2004**

**Reason for exclusion:** No useable data

**LJUBIN2000**

**Reason for exclusion:** N<10

**LLORCA2008**

**Reason for exclusion:** Open-label

**LOEBEL2007**

**Reason for exclusion:** Open-label

**LUTHRINGER2007A**

**Reason for exclusion:** No relevant comparisons

**MCELROY2007**

**Reason for exclusion:** - participants all had bipolar disorder not schizophrenia

**MCEVOY2003 [LIEBERMAN2003a]**

**Reason for exclusion:** Conference abstract

**MCEVOY2007B**

**Reason for exclusion:** No relevant comparisons

**MCGURK2005B**

**Reason for exclusion:** - Poor study quality
- High attrition due to assessor error
- Missing data particularly for the most severely ill patients
- Large group differences

**MELTZER2005A**

**Reason for exclusion:** Not an RCT

**MIZRAHI2007**

**Reason for exclusion:** Not an RCT

No relevant comparison

**MOLLER2004**

**Reason for exclusion:** No relevant comparison - placebo controlled trial

**MORI2004**

**Reason for exclusion:** - Study looked at switching

**NABER2005B**

**Reason for exclusion:** Dosing issues

**NARENDRAN2003**

**Reason for exclusion:** Letter to editor

**PAE2007**

**Reason for exclusion:** Open-label

**PEREZINGLESIAS2007**

**Reason for exclusion:** Open-label

**PEREZINGLESIAS2008**

**Reason for exclusion:** Open-label

**PEUSKENS2007**

**Reason for exclusion:** Drug not licensed in the UK

**POPOVIC2007**

**Reason for exclusion:** No relevant comparison

**POTKIN2006**

**Reason for exclusion:** 2-week data reported, then a 2nd antipsychotic added

**RIEDEL2007C**

**Reason for exclusion:** Review of Quetiapine

**ROBINSON2006**

**Reason for exclusion:** Open-label

**RUBIN2008**

**Reason for exclusion:** Study assesses sex differences in response - no relevant comparison

**RUPNOW2007**

**Reason for exclusion:** Polypharmacy - outside scope

**SACCHETTI2004**

**Reason for exclusion:** Not an RCT - before-after study

**SACCHETTI2008**

**Reason for exclusion:** Open-label

**SADDICHHA2007**

**Reason for exclusion:** Not properly randomised

**SADDICHHA2008A**

**Reason for exclusion:** Not properly randomised

**SADDICHHA2008B**

**Reason for exclusion:** Not properly randomised

**SADDICHHA2008C**

**Reason for exclusion:** Not properly randomised

**SERGI2007A**

**Reason for exclusion:** Does not meet eligibility criteria for acute, promoting recovery or treatment resistant reviews, no appropriate data for AE analysis

**SERGI2007B**

**Reason for exclusion:** Does not meet eligibility criteria for acute, promoting recovery or treatment resistant reviews, no appropriate data for AE analysis

**SUZUKI2007**

**Reason for exclusion:** Open-label

**SVESTKA2007**

**Reason for exclusion:** Open-label

**TANIGUCHI2006**

**Reason for exclusion:** Not an RCT - before-after study

**TAYLOR2007**

**Reason for exclusion:** Open-label

**TAYMEEYAPRADIT2002**

**Reason for exclusion:** Augmentation of non-AP

**TRANJOHNSON2007**

**Reason for exclusion:** - Rapid tranquilisation study

**TZIMOS2008**

**Reason for exclusion:** Open-label

**VANBRUGGEN2003**

**Reason for exclusion:** Open-label

**VOLAVKA2005**

**Reason for exclusion:** Letter to editor

**VORUGANTI2002**

**Reason for exclusion:** Non-RCT

**VORUGANTI2007**

**Reason for exclusion:** Open-label

**WOLF2007**

**Reason for exclusion:** Open-label

**WRIGHT2003A[WRIGHT2001]**

**Reason for exclusion:** - Rapid tranquilisation study

**YAMASHITA2004**

**Reason for exclusion:** - Study compared 3 licensed and one unlicensed drug
- no reason given for switching drugs
- problems with baseline data

**YAMASHITA2005[YAMASHITA2004]**

**Reason for exclusion:** - primary paper excluded
- subset analysis

**ZHU2008**

**Reason for exclusion:** Non-RCT

## References of excluded studies (update)

Arnould,B. (2002) Antipsychotics and quality of life among stable schizophrenia patients. *European Neuropsychopharmacology; 15th International Congress of the European College of Neuropsychopharmacology*, October 5 9, Barcelona, Spain 12: S310.

Arranz,B.; San,L.; Due¤as,R.M.; Centeno,M.; Ramirez,N.; Salavert,J.; Del,Moral E. (2007) Lower weight gain with the orally disintegrating olanzapine than with standard tablets in first-episode never treated psychotic patients. *Human Psychopharmacology* 22: 11 - 15.

Ascher-Svanum,H.; Stensland,M.D.; Zhao,Z.; Kinon,B.J. (2005) Acute weight gain, gender, and therapeutic response to antipsychotics in the treatment of patients with schizophrenia. *BMC Psychiatry.* 5: 13.

Assion,H.J.; Reinbold,H.; Lemanski,S.; Basilowski,M.; Juckel,G. (2008) Amisulpride augmentation in patients with schizophrenia partially responsive or unresponsive to clozapine. A randomized, double-blind, placebo-controlled trial. *Pharmacopsychiatry*. 41(1): 24 - 28.

Bellack,A.S.; Schooler,N.R.; Marder,S.R.; Kane,J.M.; Brown,C.H.; Yang,Y. (2004) Do clozapine and risperidone affect social competence and problem solving?. *American Journal of Psychiatry*. 161(2): 364 - 367.

Bender,S.; Dittmann-Balcar,A.; Schall,U.; Wolstein,J.; Klimke,A.; Riedel,M.; Vorbach,E.U.; Kuhn,K.U.; Lambert,M.; Dittmann,R.W.; Naber,D. (2006) Influence of atypical neuroleptics on executive functioning in patients with schizophrenia: a randomized, double-blind comparison of olanzapine vs. clozapine. *International Journal of Neuropsychopharmacology.* 9(2): 135 - 145.

Boggs,D.L.; Kelly,D.L.; Feldman,S.; McMahon,R.P.; Nelson,M.W.; Yu,Y.; Conley,R.R. (2008) Quetiapine at high doses for the treatment of refractory schizophrenia. *Schizophrenia Research* 101(1-3): Apr08 - 348.

Boulay LJ, Labelle A, Bourget D, Robertson S, Habib R, Tessier P, Tombaugh T, Milin R. (2007) Dissociating medication effects from learning and practice effects in a neurocognitive study of schizophrenia: Olanzapine versus haloperidol.. *Cognitive Neuropsychiatry*. 12(4): 322-328.

Buchanan,R.W.; Javitt,D.C.; Marder,S.R.; Schooler,N.R.; Gold,J.M.; McMahon,R.P.; Heresco-Levy,U.; Carpenter,W.T. (2007) The Cognitive and Negative Symptoms in Schizophrenia Trial (CONSIST): the efficacy of glutamatergic agents for negative symptoms and cognitive impairments. *American Journal of Psychiatry.* 164(10): 1593 - 1602.

Byerly,M.J.; Nakonezny,P.A.; Rush,A.J. (2008) Sexual functioning associated with quetiapine switch vs. risperidone continuation in outpatients with schizophrenia or schizoaffective disorder: A randomized double-blind pilot trial. *Psychiatry Research.* 159(1-2); 115-120.

Chaplin,R. (2007) Risperidone improves symptoms in people who are hospitalised during an acute exacerbation of schizophrenia. *Evidence-Based Mental Health.* 10(1): 15.

Chawla,B.; Luxton-Andrew,H. (2008) Long-term weight loss observed with olanzapine orally disintegrating tablets in overweight patients with chronic schizophrenia. A 1 year open-label, prospective trial. *Human Psychopharmacology.* 23(3): 211 - 216.

Chiaie,R.D.; Salviati,M.; Fiorentini,S.; Biondi,M. (2007) Add-on mirtazapine enhances effects on cognition in schizophrenic patients under stabilized treatment with clozapine. *Experimental and Clinical Psychopharmacology.* 15(6): 563-8.

Ciudad,A.; Haro,J.M.; Alonso,J.; Bousono,M.; Suarez,D.; Novick,D.; Gilaberte,I. (2008) The Schizophrenia Outpatient Health Outcomes (SOHO) study: 3-year results of antipsychotic treatment discontinuation and related clinical factors in Spain. *European Psychiatry: the Journal of the Association of European Psychiatrists*. 23(1): 1 - 7.

Ciudad,A.; Olivares,J.M.; Bousono,M.; Gomez,J.C.; Alvarez,E. (2006) Improvement in social functioning in outpatients with schizophrenia with prominent negative symptoms treated with olanzapine or risperidone in a 1 year randomized, open-label trial. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 30(8): 1515–1522.

Cortese,L.; Caligiuri,M.P.; Williams,R.; Schieldrop,P.; Manchanda,R.; Malla,A.; Harricharan,R. (2008) Reduction in neuroleptic-induced movement disorders after a switch to quetiapine in patients with schizophrenia. *Journal of Clinical Psychopharmacology.* 28(1): 69 - 73.

Crespo-Facorro,B.; Carrasco-Marin,E.; Perez-Iglesias,R.; Pelayo-Teran,J.M.; Fernandez-Prieto,L.; Leyva-Cobian,F.; Vazquez-Barquero,J.L. (2006) Interleukin-12 plasma levels in drug-naive patients with a first episode of psychosis: Effects of antipsychotic drugs. *Psychiatry Research*. 158(2); 206-216.

Crespo-Facorro,B.; Pelayo-Teran,J.M.; Perez-Iglesias,R.; Ramirez-Bonilla,M.; Martinez-Garcia,O.; Pardo-Garcia,G.; Vazquez-Barquero,J.L. (2007) Predictors of acute treatment response in patients with a first episode of non-affective psychosis: sociodemographics, premorbid and clinical variables. *Journal of Psychiatric Research*. 41(8): 659 - 666.

Crespo-Facorro,B.; Perez-Iglesias,R.; Ramirez-Bonilla,M.; Martinez-Garcia,O.; Llorca,J.; Vazquez-Barquero,J.L. (2006) A practical clinical trial comparing haloperidol, risperidone, and olanzapine for the acute treatment of first-episode nonaffective psychosis. Journal of Clinical Psychiatry. 67(10); 1511-21.

Daniel,D.G.; Currier,G.W.; Zimbroff,D.L.; Allen,M.H.; Oren,D.; Manos,G.; McQuade,R.; Pikalov,A.A.; Crandall,D.T. (2007) Efficacy and safety of oral aripiprazole compared with haloperidol in patients transitioning from acute treatment with intramuscular formulations. *Journal of Psychiatric Practice*. 13(3): 170 - 177.

de Leon,J.; Diaz,F.J.; Josiassen,R.C.; Cooper,T.B.; Simpson,G.M. (2007) Weight gain during a double-blind multidosage clozapine study. *Journal of Clinical Psychopharmacology* 27: 22 - 27.

De Leon,J.; Diaz,F.J.; Josiassen,R.C.; Simpson,G.M. (2004) Possible individual and gender differences in the small increases in plasma prolactin levels seen during clozapine treatment. *European Archives of Psychiatry and Clinical Neuroscience*. 254: 318 - 325.

De Leon,J.; Odom White,A.; Josiassen,R.C.; Diaz,F.J.; Cooper,T.B.; Simpson,G.M. (2003) Serum antimuscarinic activity during clozapine treatment. *Journal of Clinical Psychopharmacology*. 23: 336 - 341.

De Lima,M.S.; De Jesus,Mari J.; Breier,A.; Costa,A.M.; De Sena,E.P.; Hotopf,M. (2005) Quality of life in schizophrenia: A multicenter, randomized, naturalistic, controlled trial comparing olanzapine to first-generation antipsychotics. *Journal of Clinical Psychiatry*. 66(7); 831-838.

De Haan, L.; Beuk,N.; Hoogenboom,B.; Dingemans,P.; Linszen,D. (2002) Obsessive-compulsive symptoms during treatment with olanzapine and risperidone: a prospective study of 113 patients with recent-onset schizophrenia or related disorders. *Journal of Clinical Psychiatry*. 63: 104 - 107.

De Haan, L.; Van,Bruggen M.; Lavalaye,J.; Booij,J.; Dingemans,P.M.; Linszen,D. (2003) Subjective experience and D2 receptor occupancy in patients with recent-onset schizophrenia treated with low-dose olanzapine or haloperidol: a randomized, double-blind study. *American Journal of Psychiatry*. 160(2): 303 - 309.

Edwards,J.; Wong,L.; Burnett,P.; Harrigan,S.M.; McGorry,P.D.; Wade,D.; Murphy,B.; Drew,L.; Albiston,D. (2003) Enduring positive symptoms in first episode psychosis: A randomised controlled trial of clozapine and CBT. *Schizophrenia Research* 60: 321.

Faries,D.E.; Ascher-Svanum,H.; Nyhuis,A.W.; Kinon,B.J. (2008) Switching from risperidone to olanzapine in a one-year, randomized, open-label effectiveness study of schizophrenia. *Current Medical Research and Opinion*. 24(5): 1399-1405.

Feldman,P.D.; Kaiser,C.J.; Kennedy,J.S.; Sutton,V.K.; Tran,P.V.; Tollefson,G.D.; Zhang,F.; Breier,A. (2003) Comparison of risperidone and olanzapine in the control of negative symptoms of chronic schizophrenia and related psychotic disorders in patients aged 50 to 65 years. *Journal of Clinical Psychiatry*. 64(9): 998 - 1004.

Friedman,J.I.; Carpenter,D.; Lu,J.; Fan,J.; Tang,C.Y.; White,L.; Parrella,M.; Bowler,S.; Elbaz,Z.; Flanagan,L.; Harvey,P.D. (2008) A pilot study of adjunctive atomoxetine treatment to second-generation antipsychotics for cognitive impairment in schizophrenia. *Journal of Clinical Psychopharmacology*. 28(1): 59 -63.

Gallhofer,B.; Jaanson,P.; Mittoux,A.; Tanghoj,P.; Lis,S.; Krieger,S. (2007) Course of recovery of cognitive impairment in patients with schizophrenia: a randomised double-blind study comparing sertindole and haloperidol. *Pharmacopsychiatry*. 40(6): 275 - 286.

Ganesan,S.; Agambaram,V.; Randeree,F.; Eggens,I.; Huizar,K.; Meulien,D.; Study 147 Investigators (2008) Switching from other antipsychotics to once-daily extended release quetiapine fumarate in patients with schizophrenia. *Current Medical Research and Opinion*. 24(1): 21 - 32.

Genc,Y.; Taner,E.; Candansayar,S. (2007) Comparison of clozapine-amisulpride and clozapine-quetiapine combinations for patients with schizophrenia who are partially responsive to clozapine: a single-blind randomized study. *Advances in Therapy*. 24(1): 1 - 13.

Gharabawi,G.; Bossie,C.; Turkoz,I.; Kujawa,M.; Mahmoud,R.; Simpson,G. (2007) The impact of insight on functioning in patients with schizophrenia or schizoaffective disorder receiving risperidone long-acting injectable. *Journal of Nervous & Mental Disease.* (195): 976-82.

Gharabawi,G.M.; Greenspan,A.; Rupnow,M.F.T.; Kosik-Gonzalez,C.; Bossie,C.A.; Zhu,Y.; Kalali,A.H.; Awad,A.G. (2006) Reduction in psychotic symptoms as a predictor of patient satisfaction with antipsychotic medication in schizophrenia: Data from a randomized double-blind trial. *BMC Psychiatry.* 6; 45.

Goff,D.C.; Lamberti,J.S.; Leon,A.C.; Green,M.F.; Miller,A.L.; Patel,J.; Manschreck,T.; Freudenreich,O.; Johnson,S.A. (2008) A placebo-controlled add-on trial of the Ampakine, CX516, for cognitive deficits in schizophrenia. *Neuropsychopharmacology.* 33(3), 465-472.

Golden,G.; Honigfeld,G. (2008) Bioequivalence of clozapine orally disintegrating 100-mg tablets compared with clozapine solid oral 100-mg tablets after multiple doses in patients with schizophrenia. *Clinical Drug Investigation.* 28(4): 231 - 239.

Goldstein,J.M.; Cohen,L.S.; Horton,N.J.; Lee,H.; Andersen,S.; Tohen,M.; Crawford,A.; Tollefson,G. (2002) Sex differences in clinical response to olanzapine compared with haloperidol. *Psychiatry Research.* 110(1): 27 - 37.

Guz,H.; Ozkan,A. (2002) Comparison of risperidone and olanzapine in schizophrenia. *Ondokuz Mayis Universitesi Tip Dergisi* 19: 51 - 57.

Habil,M.H.; Gondoyoewono,H.; Chaudhry,H.R.; Samanwongthai,U.; Hamid,A.R.; Hashmi,I.T.; Budiman,R.; Knowles,A.G.; Buenaventura,R. (2007) Effectiveness and safety of olanzapine in the treatment of Asian outpatients with schizophrenia. *International Journal of Clinical Pharmacology & Therapeutics*. 45(12): 631 - 642.

Haro,J.M.; Suarez,D.; Novick,D.; Brown,J.; Usall,J.; Naber,D.; SOHO-Study-Group (2007) Three-year antipsychotic effectiveness in the outpatient care of schizophrenia: observational versus randomized studies results. *European Neuropsychopharmacology* 17: 235 - 244.

Haro,J.Maria; Edgell,E.T.; Novick,D.; Alonso,J.; Kennedy,L.; Jones,P.B.; Ratcliffe,M.; Breier,A. (2005) Effectiveness of antipsychotic treatment for schizophrenia: 6-month results of the Pan-European Schizophrenia Outpatient Health Outcomes (SOHO) study. *Acta Psychiatrica Scandinavica* 111(3):231.

Harvey,P.D.; Napolitano,J.A.; Mao,L.; Gharabawi,G. (2003) Comparative effects of risperidone and olanzapine on cognition in elderly patients with schizophrenia or schizoaffective disorder. *International Journal of Geriatric Psychiatry.* 18(9): 820 - 829.

Hashimoto,K.; Sudo,T.; Hirano,M.; Motomura,H.; Tagawa,K.; Nashiro,S.; Uemura,K.; Yoshimoto,S. (2006) Efficacy and safety of zotepine for patients with treatment-resistant schizophrenia. *Schizophrenia Research.* 87(1-3): 332 - 333.

Hertling,I.; Dvorak,A.; Glaser,T.; Philipp,M.; Beneke,M.; Ramskogler,K.; Walter,H.; Lesch,O.M. (2003) Influence of psychopathological symptoms on subjective quality of life of schizophrenic patients. *Psychopharmakotherapie* 10: 151 - 158.

Hirsch,S.R.; Kissling,W.; Bauml,J.; Power,A.; O'Connor,R. (2002) A 28-week comparison of ziprasidone and haloperidol in outpatients with stable schizophrenia. *Journal of Clinical Psychiatry*. 63(6): 516 - 523.

Huang,C.L.; Su,K. P.; Hsu,H. B.; Pariante,C.M. (2007) A pilot observational crossover study of QTc interval changes associated with switching between olanzapine and risperidone. *Journal of Clinical Psychiatry* 68(5): 805.

Jeste,D.V.; Barak,Y.; Madhusoodanan,S.; Grossman,F.; Gharabawi,G. (2003) International multisite double-blind trial of the atypical antipsychotics risperidone and olanzapine in 175 elderly patients with chronic schizophrenia.[erratum appears in *American Journal of Geriatric Psychiatry*. 2004 Jan-Feb;12(1):49]. *American Journal of Geriatric Psychiatry*. 11(6): 638 - 647.

Kahn,R.S.; Fleischhacker,W.W.; Boter,H.; Davidson,M.; Vergouwe,Y.; Keet,I.P.; Gheorghe,M.D.; Rybakowski,J.K.; Galderisi,S.; Libiger,J.; Hummer,M.; Dollfus,S.; Lopez-Ibor,J.J.; Hranov,L.G.; Gaebel,W.; Peuskens,J.; Lindefors,N.; Riecher-Rossler,A.; et al. (2008) Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. *Lancet*. 371(9618): 1085 - 1097.

Kahn,R.S.; Schulz,S.C.; Palazov,V.D.; Reyes,E.B.; Brecher,M.; Svensson,O.; Andersson,H.M.; Meulien,D.; Study 132 Investigators (2007) Efficacy and tolerability of once-daily extended release quetiapine fumarate in acute schizophrenia: a randomized, double-blind, placebo-controlled study. *Journal of Clinical Psychiatry.* 68(6): 832 - 842.

Keefe,R.S.; Poe,M.P.; McEvoy,J.P.; Vaughan,A. (2003) Source monitoring improvement in patients with schizophrenia receiving antipsychotic medications. *Psychopharmacology.* 169(3-4): 383 - 389.

Kelly,D.L.; Conley,R.R.; Richardson,C.M.; Tamminga,C.A.; Carpenter,W.T.,Jr. (2003) Adverse effects and laboratory parameters of high-dose olanzapine vs. clozapine in treatment-resistant schizophrenia. *Annals of Clinical Psychiatry.* 15(3-4): 181 - 186.

Kennedy,J.S.; Jeste,D.; Kaiser,C.J.; Golshan,S.; Maguire,G.A.; Tollefson,G.; Sanger,T.; Bymaster,F.P.; Kinon,B.J.; Dossenbach,M.; Gilmore,J.A.; Breier,A. (2003) Olanzapine vs haloperidol in geriatric schizophrenia: analysis of data from a double-blind controlled trial. *International Journal of Geriatric Psychiatry.* 18(11): 1013 - 1020.

Kilian,R.; Angermeyer,M.C. (2004) The impact of antipsychotic medication on the incidence and the costs of inpatient treatment in people with schizophrenia: results from a prospective observational study. *Psychiatrische Praxis*. 31: 138 - 146.

Kinon,B.J.; Ahl,J.; Rotelli,M.D.; McMullen,E. (2004) Efficacy of accelerated dose titration of olanzapine with adjunctive lorazepam to treat acute agitation in schizophrenia. *The American Journal of Emergency Medicine*. 22: 181 - 186.

Kinon,B.J.; Jeste,D.V.; Kollack,Walker S.; Stauffer,V.; Liu,Seifert H. (2004) Olanzapine treatment for tardive dyskinesia in schizophrenia patients: a prospective clinical trial with patients randomized to blinded dose reduction periods. *Progress in Neuro Psychopharmacology and Biological Psychiatry*. 28: 985 - 996.

Kinon,B.J.; Liu-Seifert,H.; Ahl,J.; Ahmed,S.; Baker,R.W. (2004) Longitudinal effect of olanzapine on fasting serum lipids: a randomized, prospective, 4-month study. *Annals of the New York Academy of Sciences*. 1032: 295 - 296.

Kluge,M.; Schuld,A.; Himmerich,H.; Dalal,M.; Schacht,A.; Wehmeier,P.M.; Hinze-Selch,D.; Kraus,T.; Dittmann,R.W.; Pollmacher,T. (2007) Clozapine and olanzapine are associated with food craving and binge eating: results from a randomized double-blind study. *Journal of Clinical Psychopharmacology*. 27(6): 662 - 666.

Krakowski,M.I.; Czobor,P.; Citrome,L.; Bark,N.; Cooper,T.B. (2006) Atypical antipsychotic agents in the treatment of violent patients with schizophrenia and schizoaffective disorder. *Archives of General Psychiatry*. 63(6): 622 - 629.

Krivoy,A.; Weizman,A.; Laor,L.; Hellinger,N.; Zemishlany,Z.; Fischel,T. (2008) Addition of memantine to antipsychotic treatment in schizophrenia inpatients with residual symptoms: A preliminary study. *European Neuropsychopharmacology*. 18(2): 117 - 121.

Lane,H.Y.; Liu,Y.C.; Huang,C.L.; Chang,Y.C.; Liau,C.H.; Perng,C.H.; Tsai,G.E. (2008) Sarcosine (N-Methylglycine) Treatment for acute schizophrenia: a randomized, double-blind study. *Biological Psychiatry*. 63(1); 9-12.

Lasser,R.A.; Bossie,C.A.; Zhu,Y.; Gharabawi,G.; Eerdekens,M.; Davidson,M. (2004) Efficacy and safety of long-acting risperidone in elderly patients with schizophrenia and schizoaffective disorder. *International Journal of Geriatric Psychiatry*. 19: 898 - 905.

Lasser,R.A.; Bossie,C.A.; Zhu,Y.; Locklear,J.C.; Kane,J.M. (2002) Long-acting risperidone in young adults with early schizophrenia or schizoaffective illness. *Annals of Clinical Psychiatry*. 95(2); 65-71.

Lauriello,J.; Lambert,T.; Andersen,S.; Lin,D.; Taylor,C.C.; McDonnell,D. (2008) An 8-week, double-blind, randomized, placebo-controlled study of olanzapine long-acting injection in acutely ill patients with schizophrenia. Journal of Clinical Psychiatry. 69(5).

Lauriello,J.; McEvoy,J.P.; Rodriguez,S.; Bossie,C.A.; Lasser,R.A. (2005) Long-acting risperidone vs. placebo in the treatment of hospital inpatients with schizophrenia. *Schizophrenia Research*. 72(2-3): 249 - 258.

Lieberman,J.A.; Phillips,M.; Gu,H.; Stroup,S.; Zhang,P.; Kong,L.; Ji,Z.; Koch,G.; Hamer,R.M. (2003) Atypical and conventional antipsychotic drugs in treatment-naive first-episode schizophrenia: a 52-week randomized trial of clozapine vs chlorpromazine. *Neuropsychopharmacology*. 28: 995 - 1003.

Lindenmayer,J.P.; Czobor,P.; Volavka,J.; Lieberman,J.A.; Citrome,L.; Sheitman,B.; McEvoy,J.P.; Cooper,T.B.; Chakos,M. (2004) Effects of atypical antipsychotics on the syndromal profile in treatment-resistant schizophrenia. *The Journal of Clinical Psychiatry*. 65: 551 - 556.

Ljubin,Tajana; Milas,ZakicDanijela; Folnegovic-Smalc,Vera; Makaric,Gordan (2000) A preliminary study of the comparative effects of olanzapine and fluphenazine on cognition in schizophrenic patients. *Human Psychopharmacology: Clinical and Experimental* 15(7): 519.

Llorca,P.M.; Sacchetti,E.; Lloyd,K.; Kissling,W.; Medori,R. (2008) Long-term remission in schizophrenia and related psychoses with long-acting risperidone: results obtained in an open-label study with an observation period of 18 months. *International Journal of Clinical Pharmacology & Therapeutics*. 46(1): 14 - 22.

Loebel,A.D.; Khanna,S.; Rajadhyaksha,S.; Siu,C.O.; Giller,E.; Potkin,S.G. (2007) Ziprasidone in treatment-resistant schizophrenia: a 52-week, open-label continuation study. *Journal of Clinical Psychiatry.* 68(9): 1333 - 1338.

Luthringer,R.; Staner,L.; Noel,N.; Muzet,M.; Gassmann-Mayer,C.; Talluri,K.; Cleton,A.; Eerdekens,M.; Battisti,W.P.; Palumbo,J.M. (2007) A double-blind, placebo-controlled, randomized study evaluating the effect of paliperidone extended-release tablets on sleep architecture in patients with schizophrenia. *International Clinical Psychopharmacology.* 22(5): 299 - 308.

Luthringer,R.; Staner,L.; Noel,N.; Muzet,M.; Gassmann-Mayer,C.; Talluri,K.; Cleton,A.; Eerdekens,M.; Battisti,W.P.; Palumbo,J.M. (2007) A double-blind, placebo-controlled, randomized study evaluating the effect of paliperidone extended-release tablets on sleep architecture in patients with schizophrenia.[erratum appears in *International Clinical Psychopharmacology*. 2007 Nov;22(6):387]. *International Clinical Psychopharmacology.* 22(5): 299-308.

Mcelroy,S.L.; Frye,M.A.; Altshuler,L.L.; Suppes,T.; Hellemann,G.; Black,D.; Mintz,J.; Kupka,R.; Nolen,W.; Leverich,G.S.; Denicoff,K.D.; Post,R.M.; Keck,P.E. (2007) A 24-week, randomized, controlled trial of adjunctive sibutramine versus topiramate in the treatment of weight gain in overweight or obese patients with bipolar disorders. *Bipolar Disorders*. 9(4): 426 - 434.

McEvoy, J.P., Daniel, D.G., Carson, W.H., McQuade, R.D., Marcus, R.N. (2007B) A randomized, double-blind, placebo-controlled, study of the efficacy and safety of aripiprazole 10, 15 or 20mg/day for the treatment of patients with acute exacerbations of schizophrenia. *Journal of Psychiatry Research*. 41: 895-905.

McEvoy,J.; Lieberman,J.A.; Perkins,D.; Hamer,R.M.; Sharma,T.; Zipursky,R.; Kahn,R.; Gur,R.; Centorrino,F.; Glick,I. (2003) Long-term efficacy and safety of atypical and conventional antipsychotic drugs in first episode schizophrenia. *Schizophrenia Research*. 60 (1); 313.

McGurk,S.R.; Carter,C.; Goldman,R.; Green,M.F.; Marder,S.R.; Xie,H.; Schooler,N.R.; Kane,J.M. (2005) The effects of clozapine and risperidone on spatial working memory in schizophrenia. *American Journal of Psychiatry.* 162(5): 1013 - 1016.

Meltzer,H.Y. (2005) Focus on the metabolic consequences of long-term treatment with olanzapine, quetiapine and risperidone: Are there differences? International Journal of Neuropsychopharmacology. 8(2): 153-156.

Mizrahi,R.; Rusjan,P.; Agid,O.; Graff,A.; Mamo,D.C.; Zipursky,R.B.; Kapur,S. (2007) Adverse subjective experience with antipsychotics and its relationship to striatal and extrastriatal D2 receptors: a PET study in schizophrenia. *American Journal of Psychiatry* 164: 630 - 637.

Mller,H.J.; Riedel,M.; Mller,N.; Fischer,W.; Kohnen,R. (2004) Zotepine versus placebo in the treatment of schizophrenic patients with stable primary negative symptoms: a randomized double-blind multicenter trial. *Pharmacopsychiatry*. 37: 270 - 278.

Moller, H.J; et al. (2008) Short-term treatment with risperidone or haloperidol in first-episode. *International Journal of Neuropsychopharmacology* 9: 1-13.

Mori,K.; Nagao,M.; Yamashita,H.; Morinobu,S.; Yamawaki,S. (2004) Effect of switching to atypical antipsychotics on memory in patients with chronic schizophrenia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 28(4): 659 - 665.

Mortimer,A.M.; Joyce,E.; Balasubramaniam,K.; Choudhary,P.C.; Saleem,P.T.; SOLIANOL,StudyGroup (2007) Treatment with amisulpride and olanzapine improve neuropsychological function in schizophrenia. *Human Psychopharmacology*. 22(7): 445 - 454.

Naber,D.; Riedel,M.; Klimke,A.; Vorbach,E.U.; Lambert,M.; Kuhn,K.U.; Bender,S.; Bandelow,B.; Lemmer,W.; Moritz,S.; Dittmann,R.W. (2005) Randomized double blind comparison of olanzapine vs. clozapine on subjective well-being and clinical outcome in patients with schizophrenia. *Acta Psychiatrica Scandinavica* 111(2): 106 - 115.

Narendran,R.; Young,C.M.; Pristach,C.A.; Pato,M.T.; Valenti,A.M.; Fass,A.R. (2003) Efficacy of clozapine in the treatment of atypical antipsychotic refractory schizophrenia: a pilot study. *Journal of Clinical Psychopharmacology*. 23(1): 103 - 104.

Pae,C.U.; Kim,J.J.; Lee,C.U.; Lee,S.J.; Lee,C.; Patkar,A.A.; Masand,P.S.; Paik,I.H. (2007) Rapid versus conventional initiation of quetiapine in the treatment of schizophrenia: a randomized, parallel-group trial. *Journal of Clinical Psychiatry* 68: 399 - 405.

Perez-Iglesias,R.; Crespo,Facorro B.; Amado,J.A.; Garcia-Unzueta,M.T.; Ramirez-Bonilla,M.L.; Gonzalez,Blanch C.; Martinez,Garcia O.; Vazquez-Barquero,J.L. (2007) A 12-week randomized clinical trial to evaluate metabolic changes in drug-naive, first-episode psychosis patients treated with haloperidol, olanzapine, or risperidone. *Journal of Clinical Psychiatry*. 68: 1733 - 1740.

Perez-Iglesias,R.; Crespo-Facorro,B.; Martinez-Garcia,O.; Ramirez-Bonilla,M.L.; Alvarez-Jimenez,M.; Pelayo-Teran,J.M.; Garcia-Unzueta,M.T.; Amado,J.A.; Vazquez-Barquero,J.L. (2008) Weight gain induced by haloperidol, risperidone and olanzapine after 1 year: Findings of a randomized clinical trial in a drug-naive population. *Schizophrenia Research*. 99(1-3): 13-22.

Peuskens,J.; Trivedi,J.; Malyarov,S.; Brecher,M.; Svensson,O.; Miller,F.; Persson,I.; Meulien,D. (2007) Prevention of schizophrenia relapse with extended release quetiapine fumarate dosed once daily: A randomized, placebo-controlled trial in clinically stable patients. *Psychiatry*. 4(11); 34-50

Popovic,V.; Doknic,M.; Maric,N.; Pekic,S.; Damjanovic,A.; Miljic,D.; Popovic,S.; Miljic,N.; Djurovic,M.; Jasovic-Gasic,M.; Dieguez,C.; Casanueva,F.F. (2007) Changes in neuroendocrine and metabolic hormones induced by atypical antipsychotics in normal-weight patients with schizophrenia. *Neuroendocrinology*. 85(4): 249 - 256.

Potkin,S.G.; Gharabawi,G.M.; Greenspan,A.J.; Mahmoud,R.; Kosik-Gonzalez,C.; Rupnow,M.F.; Bossie,C.A.; Davidson,M.; Burtea,V.; Zhu,Y.; Trivedi,J.K. (2006) A double-blind comparison of risperidone, quetiapine and placebo in patients with schizophrenia experiencing an acute exacerbation requiring hospitalization. *Schizophrenia Research.* 85(1-3): 254 - 265.

Riedel,M.; Muller,N.; Strassnig,M.; Spellmann,I.; Severus,E.; Moller,H. J. (2007) Quetiapine in the treatment of schizophrenia and related disorders. *Neuropsychiatric Disease and Treatment* 3(2): 219-235.

Robinson,D.G.; Woerner,M.G.; Napolitano,B.; Patel,R.C.; Sevy,S.M.; Gunduz-Bruce,H.; Soto-Perello,J.M.; Mendelowitz,A.; Khadivi,A.; Miller,R.; McCormack,J.; Lorell,B.S.; Lesser,M.L.; Schooler,N.R.; Kane,J.M. (2006) Randomized comparison of olanzapine versus risperidone for the treatment of first-episode schizophrenia: 4-month outcomes. *American Journal of Psychiatry* 163(12): 2102.

Rubin,L.H.; Haas,G.L.; Keshavan,M.S.; Sweeney,J.A.; Maki,P.M. (2008) Sex difference in cognitive response to antipsychotic treatment in first episode schizophrenia. *Neuropsychopharmacology.* 33(2): 290-297.

Rupnow,M.F.; Greenspan,A.; Gharabawi,G.M.; Kosik-Gonzalez,C.; Zhu,Y.; Stahl,S.M. (2007) Incidence and costs of polypharmacy: data from a randomized, double-blind, placebo-controlled study of risperidone and quetiapine in patients with schizophrenia or schizoaffective disorder. *Current Medical Research and Opinion*. 23(11): 2815 - 2822.

Sacchetti,E.; Panariello,A.; Regini,C.; Valsecchi,P. (2004) Quetiapine in hospitalized patients with schizophrenia refractory to treatment with first-generation antipsychotics: a 4-week, flexible-dose, single-blind, exploratory, pilot trial. *Schizophrenia Research*. 69(2-3): 325 - 331.

Sacchetti,E.; Valsecchi,P.; Parrinello,G. (2008) A randomized, flexible-dose, quasi-naturalistic comparison of quetiapine, risperidone, and olanzapine in the short-term treatment of schizophrenia: The QUERISOLA trial. *Schizophrenia Research*. 98(1-3): 55-65.

Saddichha,S.; Ameen,S.; Akhtar,S. (2008) Predictors of antipsychotic-induced weight gain in first-episode psychosis: conclusions from a randomized, double-blind, controlled prospective study of olanzapine, risperidone, and haloperidol. *Journal of Clinical Psychopharmacology* 28: 27 - 31.

Saddichha,S.; Manjunatha,N.; Ameen,S.; Akhtar,S. (2007) 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. *Journal of Clinical Psychiatry*. 68(11): 1793 - 1798.

Saddichha,S.; Manjunatha,N.; Ameen,S.; Akhtar,S. (2008) Diabetes and schizophrenia - effect of disease or drug? Results from a randomized, double-blind, controlled prospective study in first-episode schizophrenia. *Acta Psychiatrica Scandinavica*. 117(5): 342 - 347.

Saddichha,S.; Manjunatha,N.; Ameen,S.; Akhtar,S. (2008A) Metabolic syndrome in first episode schizophrenia - A randomized double-blind controlled, short-term prospective study. *Schizophrenia Research*. 101(1-3): 266-272.

Sergi,M.J.; Green,M.F.; Widmark,C.; Reist,C.; Erhart,S.; Braff,D.L.; Kee,K.S.; Marder,S.R.; Mintz,J. (2007) Cognition and neurocognition: effects of risperidone, olanzapine, and haloperidol. *American Journal of Psychiatry.* 164(10): 1585 - 1592.

Sergi,M.J.; Green,M.F.; Widmark,C.; Reist,C.; Erhart,S.; Braff,D.L.; Kee,K.S.; Marder,S.R.; Mintz,J. (2007) Social cognition and neurocognition: effects of risperidone, olanzapine, and haloperidol.[erratum appears in *American Journal of Psychiatry*. 2007 Nov;164(11):1766]. *American Journal of Psychiatry*. 164(10): 1585 - 1592.

Suzuki T, Uchida H, Watanabe K, Nomura K, Takeuchi H, Tomita M, Tsunoda K, Nio S, Den R, Manki H, Tanabe A, Yagi G, Kashima H. (2007) How effective is it to sequentially switch among Olanzapine, Quetiapine and Risperidone? A randomized, open-label study of algorithm-based antipsychotic treatment to patients with symptomatic schizophrenia in the real-world clinical setting. *Psychopharmacology.* 195 (2): 285-295.

Svestka,J.; Synek,O.; Tomanova,J.; Rodakova,I.; Cejpkova,A. (2007) Differences in the effect of second-generation antipsychotics on prolactinaemia: six weeks open-label trial in female in-patients. *Neuroendocrinology Letters*. 28(6): 881 - 888.

Taniguchi,T.; Sumitani,S.; Aono,M.; Iga,J.; Kinouchi,S.; Aki,H.; Matsushita,M.; Taniguchi,K.; Tsuno,M.; Yamanishi,K.; Tomotake,M.; Kaneda,Y.; Ohmori,T. (2006) Effect of antipsychotic replacement with quetiapine on the symptoms and quality of life of schizophrenic patients with extrapyramidal symptoms. *Human Psychopharmacology*. 21(7): 439 - 445.

Taylor,D. (2007) Haloperidol, olanzapine and risperidone reduce treatment failure compared to aripiprazole, quetiapine and ziprasidone in acute schizophrenia. *Evidence-Based Mental Health*. 10(3): 76.

Taymeeyapradit,U.; Kuasirikul,S. (2002) Comparative study of the effectiveness of zuclopenthixol acetate and haloperidol in acutely disturbed psychotic patients. *Journal of the Medical Association of Thailand*. 85(12): 1301 - 1308.

Tran-Johnson,T.K.; Sack,D.A.; Marcus,R.N.; Auby,P.; McQuade,R.D.; Oren,D.A. (2007) Efficacy and safety of intramuscular aripiprazole in patients with acute agitation: a randomized, double-blind, placebo-controlled trial. *Journal of Clinical Psychiatry* 68: 111 - 119.

Tzimos,A.; Samokhvalov,V.; Kramer,M.; Ford,L.; Gassmann-Mayer,C.; Lim,P.; Eerdekens,M. (2008) Safety and tolerability of oral paliperidone extended-release tablets in elderly patients with schizophrenia: A double-blind, placebo-controlled study with six-month open-label extension. *American Journal of Geriatric Psychiatry* 16(1): 31-43.

van Bruggen, J.; Tijssen,J.; Dingemans,P.; Gersons,B.; Linszen,D. (2003) Symptom response and side-effects of olanzapine and risperidone in young adults with recent onset schizophrenia. *International Clinical Psychopharmacology*. 18(6): 341 - 346.

Volavka,J.; Nolan,K.A.; Kline,L.; Czobor,P.; Citrome,L.; Sheitman,B.; Lindenmayer,J.P.; McEvoy,J.; Lieberman,J.A. (2005) Efficacy of clozapine, olanzapine, risperidone, and haloperidol in schizophrenia and schizoaffective disorder assessed with nurses observation scale for inpatient evaluation. *Schizophrenia Research*. 76: 127 - 129.

Voruganti,L.; Cortese,L.; Owyeumi,L.; Kotteda,V.; Cernovsky,Z.; Zirul,S.; Awad,A. (2002) Switching from conventional to novel antipsychotic drugs: results of a prospective naturalistic study. *Schizophrenia Research.* 57(2-3): 201 - 208.

Voruganti,L.P.; Awad,A.G.; Parker,G.; Forrest,C.; Usmani,Y.; Fernando,M.L.; Senthilal,S. (2007) Cognition, functioning and quality of life in schizophrenia treatment: results of a one-year randomized controlled trial of olanzapine and quetiapine. *Schizophrenia Research*. 96(1-3): 146 - 155.

Wolf,J.; Janssen,F.; Lublin,H.; Salokangas,R.K.; Allain,H.; Smeraldi,E.; Bernardo,M.; Millar,H.; Pans,M.; Adelbrecht,C.; Laughton,J.; Werner,C.; Maier,W. (2007) A prospective, multicentre, open-label study of aripiprazole in the management of patients with schizophrenia in psychiatric practice in Europe: Broad Effectiveness Trial with Aripiprazole in Europe (EU-BETA). *Current Medical Research and Opinion.* 23(10): 2313 - 2323.

Wright,P.; Meehan,K.; Birkett,M.; Lindborg,S.R.; Taylor,C.C.; Morris,P.; Breier,A. (2003) A comparison of the efficacy and safety of olanzapine versus haloperidol during transition from intramuscular to oral therapy. *Clinical Therapeutics*. 25(5): 1420 - 1428.

Yamashita,H.; Mori,K.; Nagao,M.; Okamoto,Y.; Morinobu,S.; Yamawaki,S. (2004) Effects of changing from typical to atypical antipsychotic drugs on subjective sleep quality in patients with schizophrenia in a Japanese population. *Journal of Clinical Psychiatry*. 65(11): 1525 - 1530.

Yamashita,H.; Mori,K.; Nagao,M.; Okamoto,Y.; Morinobu,S.; Yamawaki,S. (2005) Influence of aging on the improvement of subjective sleep quality by atypical antipsychotic drugs in patients with schizophrenia: comparison of middle-aged and older adults. *American Journal of Geriatric Psychiatry.* 13(5): 377 - 384.

Zhu,B.; scher-Svanum,H.; Shi,L.; Faries,D.; Montgomery,W.; Marder,S.R. (2008) Time to discontinuation of depot and oral first-generation antipsychotics in the usual care of schizophrenia. *Psychiatric Services*. 59(3): 315 - 317.