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.

Contents

Initial treatment with antipsychotic medication

Characteristics of included studies (previous guideline)

Study	Methods	Participants	Interventions	Outcomes
Emsley **1995**	Allocation: randomised - no further description. Blindness: double - no further information. Duration: 6 weeks. Multicentre, multinational.	Diagnosis: first-episode schizophrenia/schizophre-niform disorder (DSM-III-R). N=183. Age: range 15-50. Sex: male 122, female 61. History: age at onset of illness, median 23 (risperidone), 24 years (haloperidol).	1. Risperidone: dose mean 6.1mg/day, range 2-16mg. n=99. 2. Haloperidol: dose mean 5.6mg/day, range 1-16 mg. n=84. Flexible dose regime for both groups.	Clinical improvement (>50% in total PANSS). Global effect (CGI). Mental state (BPRS - PANSS derived, PANSS). Side effects (ESRS, specific reports). Physiological monitoring (ECG, lab tests, body weight, vital signs). Leaving the study early.
Jones1998	Allocation: random - no further details. Blindness: double. Duration: 54 weeks.	Diagnosis: schizophrenia. N=65. Setting: outpatient. Multicentre. Excluded if PANSS>90. History: 'early phase' First 5 years of illness.	One month stabilisation phase followed by a one week washout, screening period. 1. Olanzapine: dose 5-20mg daily. n=21. 2. Risperidone: dose 4-10mg daily. n=21. 3. Haloperidol: dose 5-20mg daily. n=23.	Leaving the study early. Unable to use - Mental state (PANSS, no data). Side effect (EPSRS, no data). Cost (no data). 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: - Aged 17-28 - DSM-IV criteria for schizophrenia
	Exclusion criteria: - Neurological or endocrine disease - Mental retardation - Use of adjunctive medications such as mood stabilisers or antidepressants - History of clozapine treatment - 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
	Published or unpublished data?: Published
Method	**Type of study:** Individual randomised trial
	Type of analysis: Completer
	Blindness: Double-blind
	Raters: Independent of treatment
	Design: Multi-centre - Two centres in Taipei, Taiwan
	Number of people screened, excluded & reasons: Number screened not reported.
	The study consisted of 95 healthy controls and 68 patients with schizophrenia. Out of the 68 patients, 20 were drug-naive
	Notes about study methods: The drug-naive patients were randomly divided into two groups. Randomisation procedure not reported.
	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%
	Diagnostic tool: DSM-IV
	Inclusion criteria: - PANSS Score > 65
	Total sample size: No. randomised 68 (20 of these were drug-naive).
	The study also included 95 healthy controls
	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: - Aged 16-40 - Onset of psychotic symptoms before age 35 years - Met DSM-IV criteria for schizophrenia, schizophreniform or schizoaffective disorder - Experienced psychotic symptoms for >=1 month but not more than 60 months - 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% Schizoaffective disorder - 13.5%
	Diagnostic tool: DSM-IV
	Inclusion criteria: - consenting patients aged 16-40 meeting DSM-IV criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder. - had to be in first-episode of their psychotic illness and had to be continuously ill for >=1month and no more than 5 months - PANSS >-4 on at least one psychotic item - CGI-S >=4 - 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: Risperidone: 192 days 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.

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

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

	Comments: 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: Subchronic, acute exacerbation (AE): placebo 10.3%; OLZ-L 6.2%; OLZ-M 7.8%; OLZ-H 8.7%; HAL 8.7% Chronic, AE: placebo 88.2%; OLZ-L 92.3%; OLZ-M 90.6%; OLZ-H 91.3%; HAL 91.3% Unspecified: placebo 1.5%; OLZ-L 1.5%; OLZ-M 1.6%; OLZ-H 0.0%; HAL 0.0% Inclusion/ exclusion criteria: 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. 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. Further details: Required to be hospitalised for at least 2 weeks at the beginning of the study.	Control 2: Placebo N: 68		

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

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

Carriere2000	Duration: 4 months Washout: None Concomitant medications: As required: anxiolytics, hypnotics, drugs to control incapacitating extrapyramidal symptoms, drugs for somatic disorders Comments: 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) Sex: 68% (n=136) M Illness: combined diagnoses Diagnosis: DSM-IV N: 199 Inclusion/ exclusion criteria: Participants of either sex, with paranoid schizophrenia or schizophreniform disorder. 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. Further details: 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: Amisulpride N: 94 Dose: 400-1200 mg/day oral Control: Haloperidol N: 105 Dose: 10-30 mg/day oral Intervention group n: 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%). Control group n: 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%). 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: Amisulpride is globally superior to haloperidol in the treatment of acute exacerbations of schizophrenia and significantly improves participants' quality of life and social adjustment.

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

Cetin1999	Duration: 6 weeks Washout: 1 week (placebo) Concomitant medications: Medication to control EPS and lorazepam (for sedation) were allowed Comments: Purpose of study was to determine optimal dose of risperidone	Age: not stated Sex: not stated Illness: schizophrenia Diagnosis: not stated N: 70 Duration of illness: not stated Inclusion/ exclusion criteria: not stated	Intervention: risperidone N: 50 Dose: 2mg/day (n=10); 4mg/day (n=10); 6mg/day (n=10); 8mg/day (n=10); 10mg/day (n=10) oral Control: haloperidol N: 20 Dose: 20mg/day 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: 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) Comments: Positive symptom scores were significantly lower after >=6mg doses of risperidone and 20mg haloperidol than 2 or 4mg risperidone. Negative symptom scores were lower after >=6mg risperidone than haloperidol or 2 or 4mg risperidone.

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

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

	Comments: 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: schizophrenia (n=325) or schizoaffective disorder (n=52) Inclusion/ exclusion criteria: Baseline PANSS score of 60-120, aged 18-64 years. Out-patients or in-patients hospitalised <=4weeks. 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 Further details: 79% were out-patients	Control: olanzapine N: 189 Dose: 5-20mg/day oral Intervention group n: 53/188 (adverse event 22/188) Control group n: 43/189 (adverse event 17/189)	Hallucinations: R 2, OLZ 3 Drug abuse: R 0, OLZ 3 Cardiovascular symptoms: R 0, OLZ 3 Gastrointestinal disorders: R 0, OLZ 3 Other: R 14, OLZ 21 Weight gain: R 3.4lb (SD 7.8), OLZ 7.2lb (SD 11.2) Increase in body weight of >=7%: R 18/155, OLZ 44/161 Less serious AEs: Somnolence: R 69/188, OLZ 73/189 Insomnia: R 45, OLZ 35 Headache: R 41, OLZ 32 Agitation: R 29, OLZ 40 Dry mouth: R 21, OLZ 42 Rhinitis: R 30, OLZ 31 Dizziness R 26, OLZ 27 Anxiety: R 20, OLZ 23 Vision abnormalities: R 12, OLZ 19 Extrapyramidal symptoms: R 45/188, OLZ 38/189 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.

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

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

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

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

Hale2000	**Duration:** 8 weeks **Washout:** 3-7 days **Concomitant medications:** Not stated	**Age:** Mean: 35.04 (range 17-66) years **Sex:** 400/595 M **Illness:** schizophrenia **Diagnosis:** DSM-III-R **N:** 617 **Duration of illness:** Not stated **Special characteristics:** Disorganised 82/595; Catatonic 9/595; Paranoid 305/595; Residual 52/595; Unspecified 173/595 **Inclusion/ exclusion criteria:** 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. 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:** Sertindole **N:** 492 **Dose:** 8 mg/day (n=120); 16 mg/day (n=127);20 mg/day (n=128); 24 mg/day (n=117) oral **Control:** Haloperidol **N:** 125 **Dose:** 10 mg/day oral		22 participants missing from the ITT analysis. 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. Participants in the haloperidol group received haloperidol 5mg for 3 days, then on day 4 dose was increased to 10 mg. Participants were administered matching placebo in addition to their randomised treatment, all participants took 3x tablets and 2x capsules every day.

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

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

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

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

Janicak1999 (now published as Janicak *et al*., 2001)	Duration: 6 weeks Washout: not stated Concomitant medications: not stated	Age: not stated Sex: not stated Illness: schizoaffective disorder Diagnosis: DSM-IV N: 60 Duration of illness: not stated Inclusion/ exclusion criteria: 18 years or older & have a minimum total baseline PANSS = 50. 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. Further details: There were no differences between groups on such variables as age, sex, duration or severity of psychotic symptoms.	Intervention: risperidone N: not stated Dose: up to 10mg/day oral Control: haloperidol N: not stated Dose: up to 20mg/day oral 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 ($p<0.04$). More participants on haloperidol dropped out because of side effects.	

Klieser1996	Allocation: random, no further details. Blinding: double, no further details. Duration: four weeks.	Diagnosis: schizophrenia (ICD 9), acute, paranoid hallucinatory psychoses. N=180. Age: zotepine group, mean 32.5 years; risperidone 8mg group, mean 33.1 years; haloperidol group, 33.1 years. Sex: 84 M, 96 F. 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. 2. Risperidone: increased to 4mg/day over first 7 days (not included). 3. Risperidone: increased to 8mg/day over first 7 days. 4. Clozapine: increased to 400mg/day over first 7 days (not included). 5. Remoxipride: increased to 400mg/day over first 7 days (not use). 6. Haloperidol: 15mg/day. 7. Biperiden for side effects, diazepam and chloral hydrate allowed.	Global impression (CGI). Mental state (BPRS,). Side effects (SAS, Lab tests). Cognition (SKT). Unable to use - ECG and EEG (no data). Side effects (Lab tests - no data).	
KnollCTR (Study ZT4002)	Duration: 6 months Washout: 2 weeks if MAOIs or fluoxetine had been taken.	Age: zotepine 33.5 years; haloperidol 34.8 years Sex: 94/125 M Illness: schizophrenia Diagnosis: DSM-III-R N: 125	Intervention: Zotepine N: 59 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): Aesthenia (6) Constipation (7)	

	Concomitant medications: No other antipsychotic medication was permitted except for benzodiazepines and anticholinergic drugs to control significant EPS. 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 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. 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 Control: Haloperidol N: 66 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 Intervention group n: number of dropouts = 36, AE 20, Lack of efficacy 10, stopped follow-up 1, Protocol violation 0, Other 5 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 21 participants stopped treatment due to AEs. 13 participants reported at least one serious AE - mainly related to relapse. 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) 22 participants stopped treatment due to AEs. 18 participants reported at least one serious AE - mainly related to psychiatric admissions to hospital.	

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

Liu2000	Duration: 12 weeks Washout: 1 week	Age: Mean (SD): 33.9 (10.8) years Sex: 40% male (n=15) Illness: schizophrenia Diagnosis: DSM-III-R N: 38 Duration of illness: Mean (SD): 7.8 (6.8) years Inclusion/ exclusion criteria: 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: Risperidone N: 19 Dose: not stated Control: Haloperidol N: 19 Dose: Not stated Intervention group n: 7 dropped out of the trial; 2 did not complete the Continuous Performance Test (CPT) at the end of study. Control group: 9 dropped out of the trial.	Not reported	

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

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

Marder1994	Allocation: randomised - in blocks of 12. Blindness: double - no further description. Duration: 8 weeks (preceded by 1 week washout).	Diagnosis: schizophrenia (DSM-III-R); PANSS score 60-120. N=388. Age: mean 37.4 years, range 18-65. Sex: Female 48, Male 340. 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. Setting: hospital.	1. Risperidone: dose 2mg/day. n=63. 2. Risperidone: dose 6mg/day. n=64. 3. Risperidone: dose 10mg/day. n=65. 4. Risperidone: dose 16mg/day. n=64. 5. Haloperidol: dose 20mg/day. n=66. 6. Placebo: n=66. Dose titrated, week 1 to a fixed maintenance dose. 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). Time to clinical improvement. Global effect (CGI). Mental state (BPRS, PANSS). Side effects (ESRS, modified UKU, spontaneous reports of adverse events). Physiological monitoring (ECG, lab tests). Leaving the study early.	
Mesotten1991	Allocation: randomised - no further description. Blindness: double - identical medication. Duration: 8 weeks (preceded by 1 week). 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). N=60. Age: mean 39.5 years, range 20-65. Sex: male 37, female 23. History: number of years since first hospitalisation: mean 5.7 years, range 0-38.	1. Risperidone: dose mean 9.1mg/day. n=28. 2. Haloperidol: dose mean 9.4mg/day. n=32. Individual dose titration week 1-4, fixed dose thereafter.	Global effect (CGI, subjective comparison with previous neuroleptic - investigator & recipient). Mental state (BPRS). Behaviour (NOISE). Side effects (ESRS, use of medication for EPS, specific adverse experiences). Physiological monitoring (ECG, vital signs, lab tests). Leaving the study early.	

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

	participants required immediate treatment). *Setting:* Multicentre (31 European centres in six countries between March 1993 and March 1995). Inpatients	*History:* Currently acute exacerbation of chronic or subchronic illness. Score of 12 of more on the four core BPRS productive symptoms. Not treatment-resistant. 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: Use of antiparkinsonian medication Documented EPS/ scores SAS BAS AIMS	
Muller-Siecheneder1998	Duration: 6 weeks Washout: 3 days Concomitant medications: As required: anticholinergic (biperiden) for acute dystonia and other EPS; diazepam up to 30mg/day	Age: 19-63 Sex: 60-64% F Illness: Schizoaffective/phreniform and schizophrenia Diagnosis: DSM-III-R N: 123 Duration of illness: not stated Special characteristics: 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: risperidone N: 62 Dose: 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) 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%	

	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. Inclusion/ exclusion criteria: 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. Further details: Not possible to separate results of those with major depression with psychotic features from those with schizophrenia/ affective/ phreniform disorders.	Control: Haloperidol/ amitriptyline N: 61 Dose: 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) oral Intervention group n: 15 dropouts before 3 weeks, 20 before end of study. 13 side-effects, 7 insufficient response (9 protocol deviations) Control group n: 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.	

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

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

Puech1998	*Allocation:* Random – no further details. *Blinding:* Double – no further details. *Duration:* 4 weeks, preceded by a washout period of 3-7 days. *Setting:* In-patients.	*Diagnosis:* Schizophrenia (DSM-III-R), disorganised (50%), paranoid (24%) or undifferentiated (26%) types. *Age:* Mean 36 years. *Sex:* 197 M, 122 F *N:* 319 *History:* 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. amisulpride: dose 400mg/day b.d.. n = 64. amisulpride: dose 800mg/day b.d.. n = 65. amisulpride: dose 1200mg/day b.d.. n = 65. haloperidol: dose 16mg/day b.d. n = 64.	Leaving the study early. Global state: Response (defined as rating of 1 or 2 on CGI-I scale). Mental state: BPRS total PANSS positive subscale PANSS negative subscale Extrapyramidal side effects: Prescribed anti-parkinsonian medication. Documented EPS/ scores SAS BAS AIMS Other adverse effects: UKU side effects rating scale	

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

				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 **(now published as Addington *et al.*, 2004)**	Duration: 8 weeks Washout: minimum 3 day placebo washout Concomitant medications: 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 Sex: 72% M Illness: combined diagnoses Diagnosis: DSM-III-R N: 296 Duration of illness: mean 9 years Special characteristics: chronic or subchronic schizophrenia (88%) or schizoaffective disorder (12%). Not treatment resistant. Inclusion/ exclusion criteria: PANSS total score >=60 and score of >=4 on >=2 of PANSS core items within 25 hours of 1st dose. Aged 18-64.	Intervention: ziprasidone N: 149 Dose: 80-160mg/day (flexible dose) oral Control: risperidone N: 147 Dose: 3-5mg/day (flexible dose) oral	Withdrawals: Intervention group n: Total 55/149 (AE 7, response 22, other 26) Control group n: Total 43/147 (AE 11, response 12, other 20)	

	Use of other neuroleptics, antidepressants, lithium and other mood stabilisers was prohibited. 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. Further details: Patients remained in hospital for days 1-14 but could be discharged after this			

StudyR-0548 (now published as Simpson et al., 2004)	Duration: 6 weeks Washout: 1 day Concomitant medications: 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) Sex: 176 M, 93 F Illness: combined diagnoses Diagnosis: DSM-IV N: 269 Duration of illness: 13.3 - 14.6 years Special characteristics: schizophrenia (170) or schizoaffective disorder (99), chronic or subchronic, requiring inpatient hospitalisation Inclusion/ exclusion criteria: 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: ziprasidone N: 136 Dose: 80mg/day days 1-2, 160mg/day days 3-7 then flexible dose Route: oral Control: olanzapine N: 133 Dose: 20mg days 1-2, 40mg days 3-7, then flexible dose Route: oral	Withdrawals: Intervention group n: 66/136 (adverse events 10, lack of efficacy 12) Control group n: 49/133 (adverse events 4, lack of efficacy 11)	

Szafranski1999	Duration: 18 weeks	Age: Not stated Sex: Not stated Illness: schizophrenia Diagnosis: DSM-IV N: 95 Duration of illness: Not stated Inclusion/ exclusion criteria: Not stated	Intervention: Olanzapine N: not stated Dose: 5-20 mg Control: Perphenazine N: not stated Dose: 8-40 mg Intervention group n: 56 participants completed the DAI-30 at the end of the study. 30 participants in the olanzapine group and 26 in the perphenazine group. Control group n: 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.	

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

	Comments: Maintenance phase was double blind. Predefined level of response.		Intervention group n: 69.4% completed the acute phase, 52.0% completed the maintenance phase Control group n: 53.9% completed the acute phase (p<0.001), 35.6% completed the maintenance phase (p=0.005)		
Hamilton2000 (secondary to Tollefson 1997)	Duration: 6 week acute phase followed by 46 week maintenance phase Washout: yes; length not stated Concomitant medications: Only benzodiazepines for sedation and biperiden or benztropine mesylate for EPS.	Age: Mean (SD): 38 (12) years Sex: 61.1% M Illness: combined diagnoses Diagnosis: DSM-III-R N: 778 Duration of illness: Mean (SD): 13.4 (10.8) years Inclusion/ exclusion criteria: 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. Exclusion: Documented treatment-resistance to neuroleptic agents,	Intervention: Olanzapine N: 520 Dose: 5-20 mg/day Control: Haloperidol N: 258 Dose: 5-20 mg/day Intervention group n: 319/520 participants continued on to the maintenance phase. Acute phase completion	Not reported	

	Comments: 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. Further details: 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%. Reasons: lack of efficacy (17.9%); adverse event (3.7%); participant decision (3.5%). Maintenance phase completion rate: 52.0%. Reasons: adverse events (12.9%); participant decision (10.7%); lack of efficacy (12.5%) Control group n: 104/258 participants continued on to the maintenance phase. Acute phase completion rate: 53.9% (p<0.001) Reasons: lack of efficacy (23.3%, p=0.085); adverse event (8.9%, p=0.004); participant decision (7.8%, p=0.013). Maintenance phase completion rate: 35.6%, p=0.005. Reasons: adverse events (26.0%, p=0.003); participant decision (19.2%, p=0.08); lack of efficacy (10.6%, p=0.729).		

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

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

Ziegler1989	Duration: 4 weeks Washout: 3 days Concomitant medications: not stated	Age: mean 35.5 years Sex: not stated Illness: schizophrenia Diagnosis: ICD-9 N: 40 Duration of illness: not stated Special characteristics: Paranoid and/or delusional disorders. First episode and chronic schizophrenia, positive and negative symptoms. Inclusion/ exclusion criteria: 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: amisulpride N: 20 Dose: 600mg/day (10) 300-750mg/day (10) oral Control: Haloperidol N: 20 Dose: 12mg/day (10) 2.5-22.5 mg/day (10) oral 1 participant receiving haloperidol was withdrawn early.	Webster scale score (cases of EPS): Amisulpride 4/20 Haloperidol 11/20 ($p<0.05$)	

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: - Female - Aged 18–45 - 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: - Severe physical illness - History of alcohol and substance abuse or dependence - Presence of any endocrinologic state - Taking oral contraceptives.
	Total sample size: No. randomised 35
	Gender: % female 100%
	Age: Mean Quetiapine: 27.62 (9.23) Haloperidol: 29.44 (10.08)
	Ethnicity: Not mentioned

	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: - Aged 18-65 - DSM-IV schizophrenia of the paranoid, disorganised, catatonic or undifferentiated type. - Baseline score >2 for at least two of the four PANSS items and with a sum of any two of these four items >=8 - At least moderately ill on the CGI-S - Antipsychotic-treatment naive or had shown a beneficial response to such treatment at any time in the past 5 years.
	Exclusion criteria: - 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

	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: - >=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?: +

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: - If female: non-pregnant, non-lactating and using suitable contraceptive measures - Aged 18-65 - Primary DSM-IV diagnosis of schizophrenia or schizoaffective disorder - 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 - PANSS Total >=60, and >=4 (moderate) on any two of the items on the Psychotic subscale. - 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 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: - Age 18-65 - DSM-IV schizophrenia - Experiencing acute relapse - History of previous response to antipsychotics other than clozapine and not considered refractory to typical antipsychotic medication - History of continuous treatment on an outpatient basis for at least one 3-month period during past year - PANSS Total >=60 with any two psychosis items >=4 - Medically stable as determined by physical examination, ECG and routine lab testing (including serum chemistry, urine toxicology and pregnancy test)
	Exclusion criteria: - Suicidal ideation, or considered to be at significant risk of suicide - 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: - Age 18-65 - DSM-IV schizophrenia - BPRS >=18 - If female of child-bearing potential, had to use a medically accepted means of contraception - 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 Philippines: n=120 Pakistan: n=60 Malaysia: n=61 Thailand: n=57 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: - >=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 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 309 provided consent and randomised 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: - 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 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) [Amisulpride / Olanzapine] 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: - Admitted for in-patient treatment with a diagnosis of Schizophrenia - Aged 18-65 - CGI =>4; PANSS =>61 -No Clozapine treatment within 3 months prior to study
	Exclusion criteria: - History of CNS trauma, epilepsy, meningoencephalitis, instable somatic condition, substance dependency - Lack of sufficient contraception in premenopausal females. - 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 Participants: people with treatment-resistant schizophrenia
Arato 1997	Allocation: randomised Participants: people with schizophrenia Interventions: ziprasidone vs. placebo
Beasley 1996b	Allocation: randomised Participants: people with schizophrenia Interventions: olanzapine vs. placebo
Beasley 1999	Allocation: randomised Participants: people with treatment-resistant schizophrenia
Bitter 1999	Allocation: randomised Participants: people with treatment-resistant schizophrenia
Bondolfi 1998	Allocation: randomised Participants: people with treatment-resistant schizophrenia
Borison 1996 (USA 006)	Allocation: randomised Participants: people with schizophrenia Interventions: quetiapine vs. placebo
Boyer 1995	Allocation: randomised Participants: people with schizophrenia Interventions: amisulpride vs. placebo
Breier 1999	Allocation: randomised Participants: people with treatment-resistant schizophrenia
Brook 1998	Allocation: randomised Participants: people with schizophrenia Interventions: ziprasidone vs. haloperidol
Buchanan 1998	Allocation: randomised Participants: people with treatment-resistant schizophrenia
Chiu 1976	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant) Interventions: clozapine vs. chlorpromazine

Chow 2000	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant) Interventions: clozapine vs. usual medication
Chowdury 1999	Allocation: randomised Participants: people with treatment-resistant schizophrenia
Ciurezu 1976	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant) Interventions: clozapine vs. haloperidol
Claghorn 1987	Allocation: randomised Participants: people with treatment-resistant schizophrenia
Cooper 1999b	Allocation: randomised Participants: people with schizophrenia Interventions: zotepine vs. placebo
Cosar 1999	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant) Interventions: clozapine vs. sulpiride
Covington 2000	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant) Interventions: clozapine vs. haloperidol
Daniel 1999	Allocation: randomised Participants: people with schizophrenia Interventions: ziprasidone vs. placebo
Danion 1998	Allocation: randomised Participants: people with schizophrenia Interventions: amisulpride vs. placebo
Dieterle 1999	Allocation: randomised Participants: people with schizophrenia Interventions: zotepine vs. perazine
Erlandsen 1981	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant) Interventions: clozapine vs. haloperidol
Essock 1996a	Allocation: randomised Participants: people with treatment-resistant schizophrenia

Fabre 1995 (USA 004)	Allocation: randomised Participants: people with schizophrenia Interventions: quetiapine vs. placebo
Fischer 1999	Allocation: randomised Participants: people with schizophrenia Interventions: zotepine vs. placebo
Fisher-Cornelssen 1974	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant) Interventions: clozapine vs. chlorpromazine
Fisher-Cornelssen 1976a	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant) Interventions: clozapine vs. clopenthixol
Fisher-Cornelssen 1976b	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant) Interventions: clozapine vs. trifluoperazine
Fleischhacker 1995 (Multi-country)	Allocation: randomised Participants: people with schizophrenia Interventions: quetiapine vs. quetiapine
Fleming 1998	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant) Interventions: clozapine vs. olanzapine
Gelenberg 1979b	Allocation: randomised Participants: people with treatment-resistant schizophrenia
Gerlach 1974	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant) Interventions: clozapine vs. haloperidol
Gerlach 1975	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant) Interventions: clozapine vs. haloperidol
Goff 1998	Allocation: randomised Participants: people with schizophrenia Interventions: ziprasidone vs. haloperidol
Guirguis 1977	Allocation: randomised

	Participants: people with schizophrenia (not treatment-resistant) Interventions: clozapine vs. chlorpromazine
Gunnar 1999	Allocation: randomised Participants: people with schizophrenia Interventions: ziprasidone vs. haloperidol
HGCF 2001	Allocation: randomised Participants: people with treatment-resistant schizophrenia
Hirsch 1999	Allocation: randomised Participants: people with schizophrenia Interventions: ziprasidone vs. haloperidol
Hong 1997	Allocation: randomised Participants: people with treatment-resistant schizophrenia
Honifeld 1984	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant) Interventions: clozapine vs. haloperidol
Howanitz 1999	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant) Interventions: clozapine vs. chlorpromazine
Itoh 1977	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant) Interventions: clozapine vs. haloperidol
Kane 1988	Allocation: randomised Participants: people with treatment-resistant schizophrenia
Kane 1994b	Allocation: randomised Participants: people with treatment-resistant schizophrenia
Keck 1998	Allocation: randomised Participants: people with schizophrenia Interventions: ziprasidone vs. placebo
Klieser 1989	Allocation: randomised Participants: people with treatment-resistant schizophrenia
Klieser 1994	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant) Interventions: clozapine vs. haloperidol vs. remoxipride

Kudo 1999	Allocation: randomised Participants: people with schizophrenia Interventions: quetiapine vs. mosaprimine
Kumra 1996b	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant) Interventions: clozapine vs. haloperidol
Lee 1994c	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant) Interventions: clozapine vs. various conventional antipsychotics
Leon 1974	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant) Interventions: clozapine vs. chlorpromazine
Loo 1997	Allocation: randomised Participants: people with schizophrenia Interventions: amisulpride vs. placebo
Martinot 1995	Allocation: randomised Participants: people with schizophrenia Interventions: amisulpride vs. placebo
Meyer-Lindenberg 1996	Allocation: randomised Participants: people with treatment-resistant schizophrenia
Oliemeulen 2000	Allocation: randomised Participants: people with treatment-resistant schizophrenia
Rosenheck 1997	Allocation: randomised Participants: people with treatment-resistant schizophrenia
Salganik 1998	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant) Interventions: clozapine vs. haloperidol
Sarai 1987	Allocation: randomised Participants: people with schizophrenia Interventions: zotepine vs. thioxithene
Shopsin 1979a	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant) Interventions: clozapine vs. chlorpromazine

Singer 1974	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant) Interventions: clozapine vs. chlorpromazine
Small 1997 (USA-Europe 008)	Allocation: randomised Participants: people with schizophrenia Interventions: quetiapine vs. placebo
Study 128-104 (unpublished)	Allocation: randomised Participants: people with schizophrenia Interventions: ziprasidone vs. placebo
Study 128-108 (unpublished)	Allocation: randomised Participants: people with schizophrenia Interventions: ziprasidone vs. haloperidol
Study 128-115 (unpublished)	Allocation: randomised Participants: people with schizophrenia Interventions: ziprasidone vs. haloperidol
Study 128-117 (unpublished)	Allocation: randomised Participants: people with schizophrenia Interventions: ziprasidone vs. risperidone
Study 128-301 (unpublished)	Allocation: randomised Participants: people with schizophrenia Interventions: ziprasidone vs. haloperidol
Study 128-302 (unpublished)	Allocation: randomised Participants: people with schizophrenia Interventions: ziprasidone vs. risperidone
Study 128-305 (unpublished)	Allocation: randomised Participants: people with schizophrenia Interventions: ziprasidone vs. amisulpride
Study BPI1201	Allocation: randomised Participants: people with schizophrenia Interventions: zotepine vs. placebo
Study NY-97-001 (unpublished)	Allocation: randomised Participants: people with schizophrenia Interventions: ziprasidone vs. placebo

Study R-0548 (unpublished)	Allocation: randomised Participants: people with schizophrenia Interventions: olanzapine vs. ziprasidone
Swift 1998	Allocation: randomised Participants: people with schizophrenia Interventions: ziprasidone vs. haloperidol
Tamminga 1994d	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant) Interventions: clozapine vs. haloperidol
Wahlbeck 2000	Allocation: randomised Participants: people with treatment-resistant schizophrenia
Wetzel 1991	Allocation: randomised Participants: people with schizophrenia Interventions: zotepine vs. perazine
Xu 1985	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant) Interventions: clozapine vs. chlorpromazine
Xu 1989	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant) Interventions: clozapine vs. chlorpromazine
Xu 1994	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant) 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: Blindness: Duration: 2.5 years Analysis of Drop-outs: Setting:	Diagnosis: N=365 Age: mean approx. 40 Sex: History: Stable out-patients (clinical judgement & same medication & same residence for 30 days) Exclusions:	1. Risperidone (5mg) 2. Haloperidol (5-20mg)	Relapse definition: 1. hospitalisation 2. increase of level of care and 20% PANSS increase 3. self-injury, suicidal or homicidal ideation, violent behaviour 4. CGI>6	
Speller1997	Allocation: Blindness: Duration: 52 weeks Analysis of Drop-outs: Setting:	Diagnosis: N=60 Age: mean approx 63 Sex: History: Chronic, long-term hospitalised inpatients with moderate to severe negative symptoms Exclusions:	1. Amisulpride (100-800mg) 2. Haloperidol (3-20mg)	Relapse definition: 1. increase of 3 or more BPRS positive symptom items which did not respond to a dose increase	
Tran1997	Allocation: Blindness: Duration: 28 weeks Analysis of Drop-outs: Setting:	Diagnosis: N=199 Age: not mentioned Sex: History: Initial in- or outpatients who achieved a 20% PANSS reduction Exclusions:	1. Olanzapine (10-20mg) 2. Risperidone (4-12mg)		Relapse definition: 1. Worsening of the PANSS by ≥20% and CGI≥3

Tran1998a	Allocation: Blindness: Duration: 52 weeks Analysis of Drop-outs: Setting:	Diagnosis: N=68 Age: mean approx 37 Sex: History: responders of the 6 weeks acute phase (at least 40% BPRS reduction or BPRS≥18) who were outpatients at the last visit Exclusions:	1. Olanzapine (~12mg) 2. Haloperidol (~14mg)		Relapse definition: 1. hospitalisation for psychopathology
Tran1998b	Allocation: Blindness: Duration: 52 weeks Analysis of Drop-outs: Setting:	Diagnosis: N=76 Age: mean approx 37 Sex: History: responders of the 6 weeks acute phase (at least 40% BPRS reduction or BPRS≥18) who were outpatients at the last visit Exclusions:	1. Olanzapine (~12mg) 2. Haloperidol (~14mg)		Relapse definition: 1. hospitalisation for psychopathology
Tran1998c	Allocation: Blindness: Duration: 22-84 weeks Analysis of Drop-outs: Setting:	Diagnosis: N=690 Age: mean approx 37 Sex: History: responders of the 6 weeks acute phase (at least 40% BPRS reduction or BPRS≥18) who were outpatients at the last visit Exclusions:	1. Olanzapine (5-20mg – mean 14mg) 2. Haloperidol (5-20mg – mean 13mg)		Relapse definition: 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: - 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

Study characteristics table: Relapse prevention

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: - 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 - hypersensitivity to antipsychotics; - other significant psychiatric illness; - clinically significant abnormal laboratory values; - alcohol misuse; suicide risk; - 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?: +

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: "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: - DSM-IV Axis I diagnosis other than schizophrenia, - DSM-IV Axis I diagnosis of substance dependence (except nicotine or caffeine) within 6 months before screening, - Significant risk of suicidal or aggressive behavior. - medical conditions that could potentially alter the absorption, metabolism, or excretion of the study medication; relevant history of

	significant or unstable disease; known allergic reactions to barbiturates, carbamazepine, lamotrigine, phenytoin, paliperidone, or risperidone; - previous lack of response to risperidone; - used a depot antipsychotic within 120 days or exposure to experimental treatment within 90 days before screening; - electroconvulsive treatment within 3 months before screening; or had involuntary admission to a psychiatric hospital. - 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: - aged between 18 and 55 years; - 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).

	Exclusion criteria: - any other major DSM-III-R diagnosis, - risk of suicide, alcohol or drug misuse, - Parkinson's or any other severe somatic disease, - 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: - Age 18-60 - At least two documented episodes of acute schizophrenic illness, or >=2 years of continuing psychotic symptoms - Had been outpatients for >=1 month - 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?: +

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

	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 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?: +
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) 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

Participants	**Inclusion criteria:** - completion of 6-weeks double-blind treatment with ziprasidone or olanzapine (in Simpson 2004 study) - a CGI improvement score of <=2 or a >=20% reduction in PANSS at acute-study endpoint - outpatient status
	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)
	Funding source: Pharmaceutical industry
	Published or unpublished data?: Published
Method	**Type of study:** Individual randomised trial
	Type of analysis: ITT Participants who took at least one dose of study medication and had a baseline and post-baseline assessment
	Type of analysis: LOCF
	Blindness: Double-blind
	Duration: No. weeks of treatment 6
	Raters: Not stated to be independent of treatment
	Design: Multi-centre US
	Number of people screened, excluded & reasons: 367 screened, 269 randomised and received at least one dose of study medication
	Notes about study methods: Allocation and randomisation procedures not reported
Participants	**Diagnosis:** Schizophrenia [% of sample] 63%
	Diagnosis: Other schizophrenia related [%] Schizoaffective 37%
	Diagnostic tool: DSM-IV
	Inclusion criteria: - Aged 18–55 - If female, not of childbearing potential - Have been hospitalised for no more than 2 consecutive weeks immediately before screening - Primary diagnosis of schizophrenia or schizoaffective 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 - 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: - 18-65 years; - 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 Outcomes: no compliance data reported
Daniel 1998	Interventions: Haloperidol vs. Sertindole
Essock 1996	Interventions: Clozapine vs. usual care 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
	Published or unpublished data?: Published
Method	**Type of study:** Individual randomised trial
	Type of study: Individual randomised trial (Noninferiority/equivalence)
	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. Also included a safety population defined as all randomised patients who received at least one injection.
	Blindness: Double-blind
	Duration: No. weeks of treatment 12 (prior to this was an 8-week, open-label run-in period)
	Raters: Not stated to be independent of treatment
	Design: Multi-centre 95 sites in the UK, mainland Europe, North America and Africa
	Number of people screened, excluded & reasons: 779 patients were entered into the run-in period. 137 were excluded from the double-blind treatment phase, and a further 2 randomised patients did not receive double-blind treatment.
	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%
	Diagnostic tool: DSM-IV
	Inclusion criteria: - aged 18-65 - PANSS total >=50 - no clinically relevant abnormal biochemistry, haematology or urinalysis laboratory values - 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: - Baseline Positive and Negative Syndrome Scale total scores of 60–120 - Good general health - Standard laboratory test results within reference ranges or not clinically significant.
	Exclusion criteria: - received a depot antipsychotic within 120 days of the start of the trial - were diagnosed as substance dependent, had tardive dyskinesia or a history of neuroleptic malignant syndrome - 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. Blindness: double, medication kits issues. Duration: 14 weeks (preceded by screening phase, unspecified).	Diagnosis: schizophrenia, paranoid (DSM-IV). N=28. Sex: not stated. Age: not stated. Setting: not stated. 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. 2. Haloperidol: dose range 5-20mg, mean 12.3 SD 3.3mg/day. n=25.	Leaving study early Other adverse events: COSTART list, weight change. Unable to use- Global state: CGI (no data) Mental state: BPRS, SANS (no data) Side effects: AIMS (no data)	

Anand 1998	Allocation: "randomised". Blindness: double - no further details. Duration: 12 weeks. Multicentre.	Diagnosis: schizophrenia (DSM-IV). N = 273. Sex: 78 F, 195 M. Age: mean 38.8 years. History: treatment resistant.* 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. 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. Physiological monitoring (lab tests). Mental state (PANSS, PAS, BPRS, CGI). Adverse effects.	Raw scores of the rating scales not available. Insufficient description of the dropouts - 101 participants in the risperidone group and 100 participants in the clozapine group completed the study. *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). 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. *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 Washout: 2-9 days Concomitant medications: Not stated Comments: Numbers in each group not given	Age: most >30 Sex: 59.3% M Illness: schizophrenia Diagnosis: DSM-IV N: 150 Duration of illness: Not stated. Special characteristics: Treatment-resistant or -intolerant Inclusion/ exclusion criteria: 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: Olanzapine N: not stated Dose: 10 mg/day Control: Clozapine N: not stated 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: Olanzapine demonstrated similar efficacy and safety to clozapine among participants with treatment-resistant schizophrenia.

Bondolfi 1998	Allocation: "randomly assigned", blocks of 4. Blindness: double, "double-dummy" protocol. Duration: 8 weeks (preceded by neuroleptic free period). Multicentre.	Diagnosis: schizophrenia (DSM-III-R). N=86 Sex: 25F, 61M. Age: mean 37.3 years (SD 12.6). History: moderate-severe illness, duration ill ~14 years, onset age ~26 years (SD 8.8), treatment resistant.* 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. 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. Lorazepam and oxazepam (sleep induction), biperiden and procyclidine (EPS), clothiapine (emergency treatment) as required.	Leaving the study early. Global state (CGI). Mental state (PANSS). Extrapyramidal symptoms (ESRS). 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". Blindness: double - no further details. 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). N = 29. Sex: 10 F, 19 M. Age: mean 35.0 years, range 18-55 years. History: duration ill ~12.5 years, chronic schizophrenia, partial response to neuroleptics.* 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. 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. benztropine mesylate (EPS) as required.	Leaving the study early. Physiological monitoring (lab tests). Mental state (BPRS, SANS, HDRS). Extrapyramidal side effects (modified SAS).	No dropouts after randomisation phase. *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).

Breier 2000	Duration: 6 weeks	Age: not stated Sex: not stated Illness: schizophrenia Diagnosis: not stated N: 526 Duration of illness: Special characteristics: Subpopulation of treatment-resistant participants Inclusion/ exclusion criteria: Not stated	Intervention: Olanzapine N: not stated Dose: Mean (SD) dose: 11.1 (3.4) mg/day Control: Haloperidol N: not stated Dose: Mean (SD) dose: 10.0 (3.6) mg/day	Not reported	Authors' conclusions: 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. Comments: 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. 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. Significantly greater response rates were observed in OLZ participants (47%) than HAL participants (35%) (p=0.008) in LOCF analysis.

Buchanan 1998	Randomised. Double-blind. Duration: 10 weeks (no wash-out). Setting: community.	Diagnosis: schizophrenia (DSM-III-R & SCID), chronic. 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. N=75. Sex: 23 female, 52 male. 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 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. Clinical improvement: 20% reduction in BPRS (data not reported). Acceptability: dropouts. Mental state: 18-item BPRS, SANS. Quality of life: QOLS Global functioning: Level of Functioning Scale Adverse effects: SAI, Maryland Psychiatric Research Centre Involuntary Movement Scale. Compliance.	Jadad[2] score 4. Drop-outs (n=2) excluded from results in original report have been included in present meta-analysis. Benztropine medication in group 2 may have affected results.
Chowdhury 1999	Duration: 16 weeks Washout: 7 day Concomitant medications: None reported.	Age: Mean (SD):CL 30.3 (8.78) years; RI 32.43 (9.79) years Sex: CL22/30 M; RI 23/30 M Illness: schizophrenia Diagnosis: ICD10 N: 60 Duration of illness: Mean (SD): CL 6.92 (5.07) years; 18 (4.38) years Special characteristics: Clozapine: paranoid	Intervention: Clozapine N: 30 Dose: 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. Control: Risperidone N: 30 Dose: 1mg x2 daily	Intervention group: 6 dropouts: 4 side effects; 1 refusal to do blood test; 1 lost to follow-up 8 dropouts: 3 severe akathisia; 3 inadequate response; 2 lost to follow-up Clozapine: tachycardia 76.66%; hypersalivation 60%; sedation 60%; weight gain 43.33%; constipation 30%;	Authors' conclusions: 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. Comments: 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.

		subtype 56.67% Risperidone: paranoid subtype 60% Other subtypes included hebephrenia, residual and undifferentiated. Inclusion/exclusion criteria: 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. Further details: 72 participants satisfied the inclusion criteria for the study, 9 participants did not enter the trial. 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. 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) Risperidone: constipation 50%; dry mouth 46.66%; weight gain 43.33%; akathisia 36.67%; insomnia 33.33%; tachycardia 30%; impotence 26.66%.	

Claghorn 1987	Randomised. Double-blind (identical tablets). Multi-centre. Duration: 4-8 weeks (preceded by 2 weeks wash-out). Setting: hospital.	Diagnosis: schizophrenia (DSM-II). History: Intolerant to at least two prior neuroleptics. N=151. Sex: 59 female, 92 male. 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. 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. Fixed-flexible dose schedule.	Relapse. Global effect: CGI. Acceptability: drop-outs. Mental state: 18-item BPRS. Behaviour: 30-item NOSIE. Adverse effects: AIMS, SAS (not blind).	

Conley 1998a	Allocation: randomised - no further details. Blindness: double. Duration: 8 weeks (preceded by 6/52 weeks of haloperidol & 1-2/52 washout). Investigators: trained on BPRS & SANS.	Diagnosis: schizophrenia (DSM-III-R). Inclusion criteria: minimum BPRS score of 45, CGI-S score >3, treatment resistant, non-responders during haloperidol phase. Multicentre: 3 sites. Sex: 62 M, 22 F. Setting: in hospital.	1. Olanzapine: dose 25mg/day. n=42. 2. Chlorpromazine: dose 1200mg/day & benztropine 4mg/day. n=42. Allowed benzodiazepine during washout & first 3/52 of trial.	Global state (CGI). Mental State (BPRS*, SANS). Leaving study early. Side effects (Barnes Akathisia Scale, SAS). Unable to use - Behaviour - use of benzodiazepines (no data). Hospital status (no data). Lab tests & physiological measures (no data).	*A priori efficacy >19 decrease from baseline or to <34 total score. 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; 2. No period of good functioning within the past five years; and 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.

Emsley 1999 (Multi-country 1999)	Allocation: randomised, no further details. Blindness: double-blind, no further details. 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). Inclusion criteria: persistent positive symptoms whilst previously taking antipsychotics, PANSS (P) >=15, CGI >=3. N=288. Age: mean 39 years Sex: M 203, F 85	Quetiapine 600mg/day, n=143. Haloperidol 20mg/day. n=145	Global state (CGI) Mental state (PANSS) Mental state - specific positive symptoms PANNS positive scale Mental state - specific negative symptoms PANSS negative scale Mental sate - specific mood derived BPRS mood cluster Side effects - modified Simpson-Angus Side effects - need for anticholinergic medication Leaving the study early.	

Heck 2000	Duration: 6 weeks + 1 week dose-rising phase Washout: none Concomitant medications: 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. Comments: 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) Sex: 38 M, 39 F Illness: combined diagnoses Diagnosis: DSM-III-R N: 77 Duration of illness: ?14 years Special characteristics: schizophrenia (subchronic or chronic course) or other psychotic conditions. Participants who had disturbing EPS during their previous neuroleptic treatment. Inclusion/ exclusion criteria: 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. Further details: Hospitalised, average duration 7 years.	Intervention: risperidone N: 40 Dose: flexible dose (max 16mg) oral Control: haloperidol N: 37 Dose: flexible dose (max 24mg) oral Intervention group n: 15/40 withdrew (reasons not stated) Control group n: 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.	

Hong 1997	Randomised. Double-blind. Duration: 12 weeks (preceded by a 60 mg/day haloperidol baseline period lasting up to 6 weeks) Setting: hospital.	Diagnosis: schizophrenia (DSM-IV). History: treatment-refractory* N=40. Sex: 26 female, 14 male. 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. 2) Chlorpromazine capsules: initial dose 50 mg/day for 1 week, mean dose 1163 ±228 mg/day. Max dose 1800 mg/day. n=19. Fixed-flexible dose schedule.	Acceptability: drop-outs. Mental state: PANSS, BPRS. Global effect: CGI. Improvement: decrease at least 20% in BPRS total score. 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. Multi-centre. Double-blind. Duration:6 weeks. Setting: hospital.	Diagnosis: schizophrenia (DSM-III), undifferentiated ~50%, paranoid ~33%. History: treatment-resistant*, unresponsive/ intolerant to 6 weeks haloperidol and benztropine period. N=268. Sex: 20% female, 80% male. 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. 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. Relapse. Acceptability: drop-outs. Improvement: decrease of > 20% in BPRS total score & CGI score of <3 or BPRS total score < 35. Global effect: CGI. Mental state: BPRS. Behaviour: NOSIE. 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.

Kern 1998	Duration: 8 weeks Washout: placebo washout: 3-7 days Concomitant medications: 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. Comments: 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) Sex: M:F H 25:4; R 20:7 Illness: schizophrenia Diagnosis: DSM-III-R N: 56 Duration of illness: Mean (SD): H 18.5 (7.9) years; R 19.2 (10.0) years Special characteristics: All participants included in the study were considered treatment resistant according to the criteria of Kane et al (1988). Inclusion/ exclusion criteria: Inclusion: Met the symptom severity and exclusionary criteria at the time of the initial screening (see Green at al 1997b). Further details: BPRS total scores at baseline: H 67.8 (12.0); R 63.8 (10.6) thinking disturbance: H 13.4 (3.2); R 12.6 (3.4) withdrawal/retardation: H 8.4 (3.0); 8.5 (3.2) EPS scores (SAS): H 3.1 (4.2); R 3.1 (5.2).	Intervention: Risperidone N: 27 Dose: 6 mg/day for 4 weeks flexible dose for following 4 weeks (mean = 7mg/day) Control: Haloperidol N: 29 Dose: 15 mg/day for 4 weeks flexible dose for following 4 weeks (mean = 19mg/day)	None reported.	

Klieser 1989	Double blind. Duration: 6 weeks (preceded by 14 day washout). Setting: hospital.	Diagnosis: schizophrenia - chronic treatment-resistant (no diagnostic criteria). N=32. Sex: 19 female, 11 male. History: duration of illness average 17 (SD 8) years. People on depot medication excluded. Age: average - 48 (SD 11) years	1) Clozapine: dose 400mg/day. n=16. 2) Haloperidol: dose 20mg/day. n=16. Biperiden and chloral hydrate as needed.	Relapse. Acceptability: dropouts. Global effect: CGI. Mental state: BPRS, AMDP and SANS.	
Meyer-Lindberg 1996	Allocation: random - no further details. Blinding: double - no further details. Duration: 6 weeks.	Diagnosis: schizophrenia (DSM-III-R). N=50. Age: mean ~ 33 years (SD~10). Sex: male 18 (only describe those they report on). History: unresponsive to > 3 weeks of 2 typical antipsychotics in effective doses, BPRS >39.	1. Zotepine: dose 150-450mg/day. n=25 2. Clozapine: dose 150-450mg/day. n=25.	Leaving the study early. Unable to use - Global function (CGI - no mean or SD). Mental State (BPRS, SANS - no mean or SD). Behaviour (CIPS [Collegium Internationale Psychiatriae Scalarum], NOSIE - no mean or SD) Side effects (UKU). Cognitive function (maze tests - no mean or SD). ECG (no data). Weight gain (no data).	

Oliemeulen 2000	Duration: 8 weeks	Age: not stated Sex: not stated Illness: combined diagnoses Diagnosis: DSM-IV N: 36 Duration of illness: Not stated Inclusion/ exclusion criteria: Therapy-resistant; schizophrenia or other psychotic disorders	Intervention: Olanzapine N: 21 Dose: Not stated Control: Clozapine N: 15 Dose: Not stated	None reported.	
Rosenheck 1997	Randomised. Double-blind: placebo benztropine given to clozapine group, blood counts taken from haloperidol group. Multi-centre. Duration: 1 year. Setting: Hospital and outpatient services.	Diagnosis: schizophrenia (DSM III-R & SCID). History: mean age onset 22 years, treatment-resistant, high level use of inpatient services (30-364 days of hospitalisation in preceding year. N=423. Sex: 10 female, 413 male. 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. 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. Mental state: PANSS. Improvement: decrease of >20% in PANSS total. Quality of life: Heinrichs-Carpenter Quality of Life Scale. Adverse effects: AIMS, Barnes Akathisia Scale, Simpson-Angus Scale, adverse effects checklist. Use of services: days of hospitalisation (skewed data), outpatient visits (no SD given). 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: - DSM-IV schizophrenia or schizoaffective disorder - 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: - Concurrent drug abuse or alcoholism - Organic brain disorders - Mental retardation
	Total sample size: ITT population 63
	Total sample size: No. randomised 63
	Gender: % female 26%
	Age: Mean 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: - Aged 18-65 - Met DSM-IV criteria for schizophrenia Treatment resistant as defined by: - 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. (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. 334 (80%) completed the 6-week study with only 9 (2%) discontinuing due to showing a response to treatment. 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: - 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). - patients should not have experienced satisfactory symptom relief with their most recent course of antipsychotic therapy - PANSS score >=75 and a score >=4 on at least 2 items of conceptual disorganisation, suspiciousness, hallucinatory behaviour, or delusions. - CGI-S score >=4 - Treated as an outpatient for at least 1 continuous 3-month period during the 2 years prior to entry.
	Exclusion criteria: - DSM-IV diagnosis of schizoaffective disorder, residual schizophrenia or bipolar disorder - 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 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: - Aged 18 to 60 - Met DSM-IV criteria for schizophrenia or schizoaffective disorder - 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 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: Study medications were delivered in 4-week fixed dose phase (6mg risperidone or 15mg haloperidol) followed by 4-week flexible dose phase. 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, conceptua1 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: - Aged 18+ - Primary diagnosis of schizophrenia - 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: - Aged 18-60 - DSM-IV diagnosis of schizophrenia or schizoaffective disorder - 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 - PANSS >=60
	Exclusion criteria: - 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 - 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 Participants: people with schizophrenia (not treatment-resistant)
Chow 2000	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant)
Ciurezu 1976	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant)
Cosar 1999	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant)
Covington 2000	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant)
Essock 1996	Interventions: Clozapine vs. usual care Blinding: not double-blind
Erlandsen 1981	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant)
Fisher-Cornelssen 1974	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant)
Fisher-Cornelssen 1976a	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant)
Fisher-Cornelssen 1976b	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant)
Fleming 1998	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant)

Gerlach 1974	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant)
Gerlach 1975	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant)
Guirguis 1977	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant)
Honifeld 1984	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant)
Howanitz 1999	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant)
Itoh 1977	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant)
Klieser 1994	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant)
Kumra 1996b	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant)
Lee 1994c	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant)
Leon 1974	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant)
Salganik 1998	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant)
Shopsin 1979a	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant)
Singer 1974	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant)
Tamminga 1994d	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant)
Xu 1985	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant)
Xu 1989	Allocation: randomised Participants: people with schizophrenia (not treatment-resistant)

Xu 1994	Allocation: randomised 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: Random – no further details. Blinding: Not described. Duration: 6 weeks, preceded by a 3 week washout period. Setting: Probably a single centre. Not clear whether in-patients or out-patients.	Diagnosis: Schizophrenia (DSM-III), disorganised, catatonic or residual types. Age: 21-53 Sex: 43 M, 19 F N: 62 History: Not stated (chronic?) All met Andreasen criteria for negative symptoms. Absence of marked positive symptoms. Score >7 on Defective Symptoms Assessment Scale (DSAS). Duration of illness 1-20 years (mean 9.2 years (amisulpride) and 12.3 years (fluphenazine)). 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. 2. fluphenazine: dose 2-12mg/day (flexible dose), mean = 10 mg/day. n = 28.	Leaving the study early. Mental state: BPRS global, anxiety/depression and anergia subscores; NOSIE CHESS (Clinical Hepatic Encephalopathy Staging Scale) Unable to use: Mental state: 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. Blindness: double, medication kits issued. Duration: 6 months.	Diagnosis: "schizophrenic patients with primarily negative symptoms" (DSM-IV) 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). N=245. Age: mean 37.6 years. Sex: 32% F. Setting: Inpatient or outpatient	1. Olanzapine: dose 5mg/day. n=70. 2. Olanzapine: dose 20mg/day. n=70. 3. Placebo: n=35 4. Amisulpride: dose 150mg/day. n=70.	Leaving study early. Mental state: SANS. Other adverse events: COSTART list, weight change. Quality of life: Carpenter QLS. Unable to use - Mental state: PANSS (no useable data). Side effects: extrapyramidal (no data).	
Murasaki 1999 (Japan 1999b)	Allocation: randomised, no further details. Blindness: double blind, no further details. Duration: 8 weeks (no details of washout period)	Diagnosis: schizophrenia (DSM-IV or ICD-10) Inclusion criteria: no details N=197 Age: mean 45 years Sex: M 129, F 68	Quetiapine: mean dose 226mg/day. n=100. Haloperidol: mean dose 6.7mg/day. n=97.	Mental state – general: BPRS, PANSS. Mental state – specific: PANSS-P, PANSS-N. Side-effects: extrapyramidal – the number of participants reporting EPS-related events. Leaving the study early	

Speller 1997	Allocation: Random – no further details. Blinding: Double – no further details. Duration: 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. Setting: Multicentre. 18 continuing care and rehabilitation wards at two psychiatric hospitals. Inpatients.	Diagnosis: Schizophrenia (DSM-III-R). Age: 35-76 Sex: 46M, 14F N: 60 History: 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. 2. haloperidol: dose 20mg, 16mg, 11.5mg, 8mg, 5mg, 3mg*. Dose reduced every 3 months, where possible, according to severity of symptoms. n = 31. *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 Global state: Psychotic exacerbations. Achieved or maintained low dose level at endpoint. Mental state: MS negative subscale (response and change) SANS items BPRS negative subscale MS positive subscale Side effects BARS Unable to use: 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: - Aged 18-65 - Met ICD-10 criteria F20.0-20.3, 20.5-20.9 excluding acute psychosis - Duration of illness >=2 years - 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% Schizoaffective depression 10%
	Diagnostic tool: DSM-IV
	Inclusion criteria: - Met DSM-IV criteria for schizophrenia or schizoaffective disorder - 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. 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: - primary enduring negative symptoms according to Carpenter's Criteria for the Deficit Syndrome. -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 - PANSS negative subscale score >15 - SANS total >60
	Exclusion criteria: - concurrent Axis 1 SAM-IV disorder - history of seizure disorder, or any clinically significant medical condition that would interfere with evaluations of efficacy or tolerability. - pregnancy - use of depot antipsychotic within one dosing interval - 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: - Age 18-65 years; - 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: - Substance dependence; - 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: - diagnosis of schizophrenia or schizoaffective disorder according to DSM-IV criteria - aged 18-65 - 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 - 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: - DSM-IV diagnosis of schizophrenia or schizoaffective disorder; - 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 - 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. - 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: - diagnosis of schizophrenia or schizoaffective disorder who had been receiving clozapine treatment (300-900mg/day) for >=6 months - 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. - 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
	Funding source: None declared
	Published or unpublished data?: Published
Methods	**Type of study:** Individual randomised trial
	Type of analysis: Completer - Paper unclear about method of analysis
	Blindness: Single-blind
	Duration: No. weeks of treatment - *6*
	Raters: Independent of treatment
	Design: Single-centre - Firat University School of Medicine, Elazig, Turkey
	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). - 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.
	Notes about study methods: Randomisation procedure not reported
Participants	**Diagnosis:** Schizophrenia [% of sample] 100%
	Diagnostic tool: DSM-IV
	Inclusion criteria: - DSM-IV diagnosis - Free from all medications for >=2 weeks prior to randomisation. 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)
	Exclusion criteria: - Presence of severe physical illness; history of lipid-lowering treatment, and presence of any endocrinologic disorder - 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 - Duration of symptoms <=60 months - No prior treatment with antipsychotics, or if treated, no more than 14 days over lifetime - Aged 16-40 - 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) Duration of symptoms (months): 18.4 (17.8)
	Baseline stats: BPRS 43.8 (5.1) CGI 5.6 (0.6) 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
	Global state & service outcomes: Average score/change in global state
	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)
	Mental state: Average score/change in mental state - PANSS
	Adverse events: Number of people with specific adverse effects
	Adverse events: Number of people with general adverse effects
	Other: - average change in BMI and body weight - Clinically significant BMI change defined as a change >=7% -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
	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?: >50% 72%
	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%
	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	**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 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 - DSM-IV schizophrenia or schizoaffective disorder - At high risk of suicide, defined as any of the following: 1) History of previous attempts or hospitalisations to prevent a suicide attempt in past 3 years 2) moderate or severe suicidal ideation with depressive symptoms 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% Black 15% Oriental 1% 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: - Aged 18 to 65 years of age; - Primary diagnosis of schizophrenia - Able to take oral antipsychotic medication
	Exclusion criteria: - Diagnosis of schizoaffective disorder, mental retardation, or other cognitive disorders; - history of serious AEs to the proposed treatments; - had had only one schizophrenic episode; - 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% Schizoaffective 17% Delusional disorder 4%
	Diagnostic tool: DSM-IV
	Inclusion criteria: - DSM-IV schizophrenia, schizoaffective disorder, or delusional disorder - Age 18-65 - At least 1 month since the first onset of positive psychotic symptoms - Psychiatrist electing to change the current FGA or SGA treatment because of inadequate clinical response or intolerance.
	Exclusion criteria: - Substance misuse or a medical disorder considered clinically to be the major cause of positive psychotic symptoms - 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.