NKR24 - PICO2 - Schizophrenia: Long-acting injectable antipsychotics versus oral antipsychotics

Characteristics of studies

Characteristics of included studies

Arango 2006

Methods	—sb —3 centres 52 weeks N=46
Participants	—Schizophrenia, DSM-IV, with a history of violence
Interventions	1. Zuclopenthixol i.m. (mean 233 mg biweekly) 2. Oral zuclopenthixol (mean 35 mg daily)
Outcomes	—Primary study outcome was avoidance of violence —Depot patients had more positive symptoms at baseline
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	cf. Leucht 2011
Allocation concealment (selection bias)	Low risk	cf. Leucht 2011
Blinding of participants and personnel (performance bias)	Low risk	cf. Leucht 2011
Blinding of outcome assessment (detection bias)	Low risk	cf. Leucht 2011
Incomplete outcome data (attrition bias)	Low risk	cf. Leucht 2011
Selective reporting (reporting bias)	Low risk	cf. Leucht 2011
Other bias	High risk	cf. Leucht 2011

Bai 2007

Methods	**Study design:** **Study grouping:** **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** Risperidone LAI ● *Age, mean (SD), y*: ● *Gender, % male*: ● *Age at first hospitalization, mean (SD), y*: SGA physician's choice ● *Age, mean (SD), y*: ● *Gender, % male*: ● *Age at first hospitalization, mean (SD), y*: **Included criteria:** **Excluded criteria:**
Interventions	**Intervention Characteristics** Risperidone LAI ● *Study duration*: ● *Dose*: SGA physician's choice ● *Study duration*: ● *Dose*:
Outcomes	*Dichotomous*: ● Discontinuation due to adverse events ● Hospitalization within study duration ● Adverse events ● All-cause discontinuation ● Relapse, longest time-point

	● Mortality
Identification	**Sponsorship source:** **Country:** **Setting:** **Comments:** **Authors name:** **Institution:** **Email:** **Address:**
Notes	**Identification:** **Participants:** **Study design:** **Baseline characteristics:** **Intervention characteristics:** **Pretreatment:** **Continuous outcomes:** **Dichotomous outcomes:** **Adverse outcomes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	no info
Allocation concealment (selection bias)	High risk	
Blinding of participants and personnel (performance bias)	Low risk	Quote: "ran- domized, prospective, single-blind study" Comment: Unclear how blinding was performed, but outcomes are objective in this study.. Probably low risk in this item.
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "Clinical efficacy and side effects were assessed by trained investigators at baseline and weeks 4, 8, 12, 24, 36, and 48." Comment: not described
Incomplete outcome data (attrition bias)	Low risk	Quote: "All 5 patients with- drawn from the study were from the risperidone long- acting injection group. One patient withheld informed consent due to gastrointestinal side effects at week 5, 2 patients were discharged in stable condition, and 2 pa- tients taking 25 mg risperidone long-acting injection q 2 weeks (original oral risperidone doses of 3 mg/day and 4 mg/day, respectively) had symptom relapses." Comment: Relatively small dropout. ITT analysis
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Barnes 1983

Methods	—db (double dummy) —Single-centre 52 weeks N=36
Participants	—Schizophrenia, Present State Examination —49.5
Interventions	1. Fluphenazine decanoate i.m. biweekly+ oral PBO (dose n.i., n= 19 2. Oral pimozide+ PBO i.m., (dose n.i., n= 17)
Outcomes	
Identification	
Notes	All patients were stable on fluphenazine depot (“enriched design”)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	cf. Leucht 2011
Allocation concealment (selection bias)	Unclear risk	cf. Leucht 2011
Blinding of participants and personnel (performance bias)	Low risk	cf. Leucht 2011
Blinding of outcome assessment (detection bias)	Low risk	cf. Leucht 2011

Incomplete outcome data (attrition bias)	Low risk	cf. Leucht 2011
Selective reporting (reporting bias)	Low risk	cf. Leucht 2011
Other bias	High risk	cf. Leucht 2011

Buckley 2014

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Open Label:** YES **Cluster RCT:**
Participants	**Baseline Characteristics** Risperidone LAI ● *Age, mean (SD), y*: 38.18 (11.8) ● *Gender, % male*: 71 ● *Age at first hospitalization, mean (SD), y*: 23 (9.2) SGA physician's choice ● *Age, mean (SD), y*: 38.32 (12.3) ● *Gender, % male*: 72 ● *Age at first hospitalization, mean (SD), y*: 22.6 (8.4) **Included criteria:** schizophrenia or schizoaffective disorder, 18-65 y, symptom exacerbation within 12 monhts of screening, community dwelling for at least 4 weeks, at least moderately ill (CGI 4 or above) **Excluded criteria:** first episode of psychosis, allergy to study medication, indadequate prior response to risperidone, treatment-refractoriness, lack of response to clozapine, medical instability
Interventions	**Intervention Characteristics** Risperidone LAI ● *Study duration*: Mean treatment duration for subjects was 551.2 ± 341.8 days for LAI-R ● *Dose*: LAI-R was initiated with a25-mg injection. Injectiondosage could be increased as needed to 37.5 or 50 mg orreduced to 12.5 mg.the modal dosereceived was 50 mg (38%); 37.5 mg (22.%); 25 mg (22%);12.5 mg (6%); 62.5 mg (5%); 75 mg (5%) SGA physician's choice ● *Study duration*: Mean treatment duration for subjects was 542.6 ± 335.4 days for Oral SGA ● *Dose*: risperidone was most frequentlyprescribed for 67 (44%); the mean (SD) of the modal prescribeddose was 5.1 (2.1). Olanzapine was prescribed for30 (20%), mean (SD) dose of 23 (13.6); aripiprazole for22 (14%), mean (SD) dose 23.4 (10.6); ziprasidone for14 (9%), mean (SD) dose 142.8 (56.5); paliperidone for9 (6%), mean (SD) dose 8.3 (2.9); quetiapine for 8 (5%),mean (SD) dose 525 (138.9); and iloperidone 1 (1%) dose12.
Outcomes	*Dichotomous*: ● All-cause discontinuation ● Discontinuation due to adverse events ● Hospitalization within study duration ● Relapse, longest time-point: psychiatric hospitalisation; increase in level of psychiatric care; substantial clinical deterioration as indicated by CGI-S much worse or very much worse; self-injury; suicidal or homicidal ideation ● Mortality ● Adverse events
Identification	**Sponsorship source:** NIMH **Country:** US, 8 centers **Setting:** outpatients **Comments:** **Authors name:** Peter F. Buckley **Institution:** Medical College of Georgia, Georgia Regents University, Augusta, GA **Email:** **Address:**
Notes	**Identification:** **Participants:** **Study design:** **Baseline characteristics:** **Intervention characteristics:** **Pretreatment:** **Continuous outcomes:** **Dichotomous outcomes:** **Adverse outcomes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: randomly assigned, not further specified
Allocation concealment (selection bias)	Unclear risk	Comment: Not described

Blinding of participants and personnel (performance bias)	High risk	Comment: unblinded
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: masked, centralized assessors, monitored bi-weekly by on-site clinicians and assessors who knew treatment assignment, scale of functioning completed by on-site, undblinded raters
Incomplete outcome data (attrition bias)	High risk	Comment: 48% and 51% attrition rate, not a bias for primary outcome (relapse)
Selective reporting (reporting bias)	Low risk	Comment: study protocol available at clinicaltrials.gov, no evidence of selective outcome reporting
Other bias	Low risk	Comment: No other obvious source of bias

Crawford 1974

Methods	**Study design:** **Study grouping:** **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** Risperidone LAI ● *Age, mean (SD), y*: ● *Gender, % male*: ● *Age at first hospitalization, mean (SD), y*: SGA physician's choice ● *Age, mean (SD), y*: ● *Gender, % male*: ● *Age at first hospitalization, mean (SD), y*: **Included criteria:** **Excluded criteria:**
Interventions	**Intervention Characteristics** Risperidone LAI ● *Study duration*: ● *Dose*: SGA physician's choice ● *Study duration*: ● *Dose*:
Outcomes	*Dichotomous*: ● Discontinuation due to adverse events ● Hospitalization within study duration ● Adverse events ● All-cause discontinuation ● Relapse, longest time-point ● Mortality
Identification	**Sponsorship source:** **Country:** **Setting:** **Comments:** **Authors name:** **Institution:** **Email:** **Address:**
Notes	**Identification:** **Participants:** **Study design:** **Baseline characteristics:** **Intervention characteristics:** **Pretreatment:** **Continuous outcomes:** **Dichotomous outcomes:** **Adverse outcomes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	
Allocation concealment (selection bias)	High risk	
Blinding of participants and personnel (performance bias)	Low risk	
Blinding of outcome assessment (detection bias)	Unclear risk	no info
Incomplete outcome data (attrition bias)	Unclear risk	no info
Selective reporting (reporting bias)	Low risk	

Other bias	Low risk	

Del Guidice 1975

Methods	—sb —Single-centre Terminated at 69 weeks, planned for 104 weeks Terminated at 69 weeks, planned for 104 weeks N=58
Participants	—Schizophrenia, clinical diagnosis —Range 20–50
Interventions	1. Fluphenazine enanthate+ oral PBO (25 mg biweekly) 2. Fluphenazine hydrochloride+ PBO i.m. (mean 21.7 mg daily, range 5–80 mg daily)
Outcomes	
Identification	
Notes	—Nurse 24 h available for patients —Flexible oral dose, fixed depot dose —Terminated prematurely at 69 weeks

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	cf. Leucht 2011
Allocation concealment (selection bias)	Unclear risk	cf. Leucht 2011
Blinding of participants and personnel (performance bias)	Unclear risk	cf. Leucht 2011
Blinding of outcome assessment (detection bias)	Unclear risk	cf. Leucht 2011
Incomplete outcome data (attrition bias)	Low risk	cf. Leucht 2011
Selective reporting (reporting bias)	Low risk	cf. Leucht 2011
Other bias	High risk	cf. Leucht 2011

Detke 2014

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Open Label:** YES **Cluster RCT:**
Participants	**Baseline Characteristics** Olanzapine LAI ● *Age, mean (SD), y*: 41.7 (10.9) ● *Male %*: 66.3 ● *Age of onset of schizophrenia, mean (SD), y*: 26.0 (9.2) ● *PANSS total score, mean (SD)*: 56.8 (9.8) ● *Rated by investigator as having poor adherence to medication at study entry, n (%)*: 10 (3.8) Olanzapine oral ● *Age, mean (SD), y*: 40.1 (10.8) ● *Male %*: 68.1 ● *Age of onset of schizophrenia, mean (SD), y*: 26.5 (8.7) ● *PANSS total score, mean (SD)*: 56.5 (8.7) ● *Rated by investigator as having poor adherence to medication at study entry, n (%)*: 14 (5.4) **Included criteria:** Outpatients, 18 to 65 years old,meeting criteria for schizophrenia based on the Diagnosticand Statistical Manual of Mental Disorders, Fourth Edition(DSM-IV) or the DSM-IV Text Revision. Patients were requiredto be considered ‘‘at risk for relapse,’’ defined as having experienced at least 2 episodes of clinical worsening of schizophreniasymptoms in the previous 24 months such that thepatient was hospitalized or required an increased level of caresurrounding the episode. Increased level of care could includethe addition of or change to any of the following from a lowerlevel of care: day hospital program; outpatient crisis management;short-term psychiatric treatment in an emergency department;or an addition, increase, or switch of medication.Patients were also required to be sufficiently clinically stableat the time of study entry, defined as no acute hospitalization forpsychosis in the 8 weeks before visit 1, a Positive and NegativeSyndrome Scale (PANSS) total score of lower than 70 at visits 1and 2, and a Clinical Global Impressions Severity of IllnessScale (CGI-S) of 4 or lower at visits 1 and 2. Finally, the patientand the treating physician were required to have a desire tochange the patient’s therapy due to unsatisfactory clinicalresponse, adverse events, or nonadherence to current antipsychotic therapy. **Excluded criteria:** Exclusion criteria included previous participationin studies of olanzapine LAI, treatment resistanceto olanzapine, previous withdrawal from olanzapine treatmentdue to clinically significant and/or intolerable adverseevents,

	substance dependence (other than nicotine or caffeine)within the past 30 days, pregnancy, breast-feeding,or serious or unstable medical illness
Interventions	**Intervention Characteristics** Olanzapine LAI ● *Study duration, months*: The study consisted of a 2- to 14-day screening periodfollowed by up to 2 years of randomized, open-label treatmentwith either oral or LAI olanzapine. ● *Mean dose*: 13.8 mg/day Olanzapine oral ● *Study duration, months*: The study consisted of a 2- to 14-day screening periodfollowed by up to 2 years of randomized, open-label treatmentwith either oral or LAI olanzapine. ● *Mean dose*: 10-20 mg/day
Outcomes	*Continuous*: ● Heinrichs-Carpenter Quality of Life Scale (QLS) *Dichotomous*: ● All-cause discontinuation ● Discontinuation due to adverse events ● Relapse at longest follow-up ● Mortality ● Injection-site adverse events ● Hospitalization within study duration
Identification	**Sponsorship source:** Eli Lilly, role of sponsor not explicitly described **Country:** **Setting:** Outpatients **Comments:** **Authors name:** Holland C. Detke **Institution:** Lilly Corporate Center, Eli Lilly and Company, Indianapolis, IN 46285 **Email:** **Address:**
Notes	**Identification:** **Participants:** **Study design:** **Baseline characteristics:** **Intervention characteristics:** **Pretreatment:** **Continuous outcomes:** *Lone Baandrup* QLS outcome is from Ascher-Svanum 2014 who reports on the same study (and therefore no separate risk of bias assessment for that study) **Dichotomous outcomes:** **Adverse outcomes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Randomized, not further described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias)	High risk	Comment: Unblinded
Blinding of outcome assessment (detection bias)	High risk	Comment: No methods described to blind outcome assessors, so probably undblinded
Incomplete outcome data (attrition bias)	High risk	Comment: Discontinuation rate>50%, not necessarily a problem for main outcome but for secondary measures
Selective reporting (reporting bias)	Low risk	Comment: No evidence of selective reporting, registered at clinictrials.gov
Other bias	Unclear risk	Comment: Role of funding pharmaceutical company not explicitly described

Fallon 1978

Methods	—db (double dummy) —Single-centre 52 weeks N=44
Participants	—Schizophrenia, Present State Examination —39
Interventions	1. Fluphenazine decanoate i.m.+ oral PBO (25 mg fortnightly, up to 50 mg weekly) 2. Oral pimozide+ PBO i.m.(8 mg daily, max. 16 mg daily)

Outcomes	
Identification	
Notes	—Tablet defaulting patients were a priori excluded —Nurse contacted patients who failed to attend visits —Occurred in the acute phase —The allocation of 9 dropouts is unclear

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	cf Leucht 2011
Allocation concealment (selection bias)	Unclear risk	cf Leucht 2011
Blinding of participants and personnel (performance bias)	Low risk	cf Leucht 2011
Blinding of outcome assessment (detection bias)	Low risk	cf Leucht 2011
Incomplete outcome data (attrition bias)	High risk	cf Leucht 2011
Selective reporting (reporting bias)	Low risk	cf Leucht 2011
Other bias	High risk	cf Leucht 2011

Fleischhacker 2014

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Open Label:** **Cluster RCT:**
Participants	Aripiprazole LAI 400 mg ● *Age, mean (SD), y*: 41.7 (10.4) ● *Male %*: 60.4 ● *Age of onset of schizophrenia, mean (SD), y*: 28.2 (9.3) ● *PANSS total score, mean (SD)*: 58.0 (12.9) ● *Rated by investigator as having poor adherence to medication at study entry, n (%)*: NA Aripiprazole oral ● *Age, mean (SD), y*: 41.2 (10.8) ● *Male %*: 63.2 ● *Age of onset of schizophrenia, mean (SD), y*: 26.9 (9.1) ● *PANSS total score, mean (SD)*: 56.6 (12.7) ● *Rated by investigator as having poor adherence to medication at study entry, n (%)*: NA **Included criteria:** 18–60 years and a diagnosis ofschizophrenia according to DSM-IV-TR10 criteria for more than 3 yearsand a history of symptom exacerbation when not receivingantipsychotic treatment. Patients needed to have been responsiveto antipsychotic treatment (other than clozapine) in the past year **Excluded criteria:** a DSM-IV-TR diagnosis other thanschizophrenia; uncontrolled thyroid function abnormalities; ahistory of seizures, neuroleptic malignant syndrome, clinically relevant tardive dyskinesia, or other medical condition thatwould expose the patient to undue risk or interfere with studyassessments. Patients who had been admitted to hospital,including for psychosocial reasons, for 430 days total of the90 days preceding entry into phase 1 or 2 of the study afterscreening were excluded. Individuals were also excluded if theymet DSM-IV-TR criteria for substance dependence, includingalcohol and benzodiazepines but excluding nicotine and caffeine.
Interventions	**Intervention Characteristics** Olanzapine LAI ● *Study duration, months*: ● *Mean dose*: Olanzapine oral ● *Study duration, months*: ● *Mean dose*: Aripiprazole LAI 400 mg ● *Study duration, months*: up to 38 weeks (app. 9 months) ● *Mean dose*: 400 mg/month Aripiprazole oral ● *Study duration, months*: up to 38 weeks (app. 9 months) ● *Mean dose*: 20.0 (6.9)/day
Outcomes	*Continuous*: ● Heinrichs-Carpenter Quality of Life Scale (QLS) *Dichotomous*: ● All-cause discontinuation ● Discontinuation due to adverse events ● Relapse at longest follow-up

	● Mortality ● Injection-site adverse events ● Hospitalization within study duration
Identification	**Sponsorship source:** This study was supported by Otsuka Pharmaceutical Commercialization, Inc. (Tokyo, Japan).Editorial support for the preparation of this manuscript was provided by Suzanne Patel atOgilvy Healthworld Medical Education and Amy Roth Shaberman, PhD, and Brett D. Mahon,PhD, at C4 MedSolutions, LLC, a CHC Group company; funding was provided by OtsukaPharmaceutical Commercialization, Inc. and H. Lundbeck A/S. **Country:** Multinational, 105 centres **Setting:** outpatients **Comments:** **Authors name:** W. Wolfgang Fleischhacker, **Institution:** Department of Psychiatry and Psychotherapy, Medical University Innsbruck, Innsbruck, Austria **Email:** **Address:**
Notes	**Identification:** **Participants:** **Study design:** **Baseline characteristics:** **Intervention characteristics:** **Pretreatment:** **Continuous outcomes:** **Dichotomous outcomes:** **Adverse outcomes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Not described in the text
Allocation concealment (selection bias)	Unclear risk	Comment: Not described in the text
Blinding of participants and personnel (performance bias)	Low risk	Comment: double-blinded, double-dummy approach
Blinding of outcome assessment (detection bias)	Low risk	Comment: Probably done
Incomplete outcome data (attrition bias)	Low risk	Comment: Discontinuation 26% vs. 33% after 38 weeks, considered acceptable
Selective reporting (reporting bias)	Low risk	Comment: protocol available, primary outcome changed from date of randomization, but justified due to lower-than-anticipated relapse rate
Other bias	High risk	Comment: Role of funding pharmaceutical company not clear

Gaebel 2010

Methods	—Open —Multi-centre 104 weeks, study was terminated after planned interim analysis N=710
Participants	—Schizophrenia, DSM-IV, stable under antipsychotic treatment for at least 4 weeks —41.6
Interventions	1.Risperidone i.m. (25 mg 2 weekly, increased by 12.5 mg every 4 weeks as needed, mean modal dose 33.6± 10.1 mg biweekly, n= 355) 2.Oral quetiapine (300–400 mg daily, mean modal dose 413.3 ± 159.2 mg daily, n= 355)
Outcomes	
Identification	
Notes	relapse definition: as Buckley 2014

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	cf. Leucht 2011
Allocation concealment (selection bias)	Unclear risk	cf. Leucht 2011
Blinding of participants and personnel (performance bias)	High risk	cf. Leucht 2011

Blinding of outcome assessment (detection bias)	High risk	cf. Leucht 2011
Incomplete outcome data (attrition bias)	Low risk	cf. Leucht 2011
Selective reporting (reporting bias)	Low risk	cf. Leucht 2011
Other bias	High risk	cf. Leucht 2011

Glick 2005

Methods	**Study design:** **Study grouping:** **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** Risperidone LAI ● *Age, mean (SD), y*: ● *Gender, % male*: ● *Age at first hospitalization, mean (SD), y*: SGA physician's choice ● *Age, mean (SD), y*: ● *Gender, % male*: ● *Age at first hospitalization, mean (SD), y*: **Included criteria:** **Excluded criteria:**
Interventions	**Intervention Characteristics** Risperidone LAI ● *Study duration*: ● *Dose*: SGA physician's choice ● *Study duration*: ● *Dose*:
Outcomes	*Dichotomous*: ● Discontinuation due to adverse events ● Hospitalization within study duration ● Adverse events ● All-cause discontinuation ● Relapse, longest time-point ● Mortality
Identification	**Sponsorship source:** **Country:** **Setting:** **Comments:** **Authors name:** **Institution:** **Email:** **Address:**
Notes	**Identification:** **Participants:** **Study design:** **Baseline characteristics:** **Intervention characteristics:** **Pretreatment:** **Continuous outcomes:** **Dichotomous outcomes:** **Adverse outcomes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "were randomly assigned" Comment: Unclear how randomization was done.Does not seem random?? Quote: "19 were randomly assigned to the quetiapine group, and 10 were randomly assigned to the haloperidol decanoate group." Comment: Unclear how randomization was done.
Allocation concealment (selection bias)	Unclear risk	Comment: No described, probably not done.
Blinding of participants and personnel (performance bias)	High risk	Quote: "open-label, ran- domized trial," Comment: No blinding.

Blinding of outcome assessment (detection bias)	Low risk	Quote: "All ratings were performed by clinicians who were not aware of the patient's treat- ment assignment."
Incomplete outcome data (attrition bias)	High risk	Quote: "During the first 4 weeks of the study, 3 patients dropped out. Thus, at the first postbase- line assessment (week 4), data were collected from 22 exacerbation-free patients (15 in the quetiapine group, 7 in the haloperidol decanoate group). By the final assess- ment (week 48), only 12 patients (7 in the quetiapine group, 5 in the haloperidol decanoate group) remained in the study." Comment: No intention to treat analysis.
Selective reporting (reporting bias)	Unclear risk	Comment: No protocol. Study of low quality. If outcomes seem relevant - unclear.
Other bias	Low risk	no other bias

Hogarty 1979

Methods	—db (double dummy) —Single-center 104 weeks N=105
Participants	—Schizophrenia, clinical diagnosis —34.2
Interventions	1. Fluphenazine decanoate i.m.+ oral PBO (mean 34 mg biweekly, n= 55) 2. Fluphenazine hydrochloride+ PBO i.m. (mean 9.9 mg daily, n= 50)
Outcomes	
Identification	
Notes	—13 patients left the trial after 12 months, it is unclear to which group they were assigned —Randomisation occurred in the acute phase

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	cf. Leucht 2011
Allocation concealment (selection bias)	Unclear risk	cf. Leucht 2011
Blinding of participants and personnel (performance bias)	Unclear risk	cf. Leucht 2011
Blinding of outcome assessment (detection bias)	Unclear risk	cf. Leucht 2011
Incomplete outcome data (attrition bias)	Low risk	cf. Leucht 2011
Selective reporting (reporting bias)	High risk	cf. Leucht 2011
Other bias	High risk	cf. Leucht 2011

Kane 2010

Methods	**Study design:** **Study grouping:** **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** Risperidone LAI ● *Age, mean (SD), y*: ● *Gender, % male*: ● *Age at first hospitalization, mean (SD), y*: SGA physician's choice ● *Age, mean (SD), y*: ● *Gender, % male*: ● *Age at first hospitalization, mean (SD), y*: **Included criteria:** **Excluded criteria:**
Interventions	**Intervention Characteristics** Risperidone LAI ● *Study duration*: ● *Dose*: SGA physician's choice ● *Study duration*: ● *Dose*:

Outcomes	*Dichotomous*: ● Discontinuation due to adverse events ● Hospitalization within study duration ● Adverse events ● All-cause discontinuation ● Relapse, longest time-point ● Mortality
Identification	**Sponsorship source:** **Country:** **Setting:** **Comments:** **Authors name:** **Institution:** **Email:** **Address:**
Notes	**Identification:** **Participants:** **Study design:** **Baseline characteristics:** **Intervention characteristics:** **Pretreatment:** **Continuous outcomes:** **Dichotomous outcomes:** **Adverse outcomes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned, in a 1:1:2:1:2 ratio,"
Allocation concealment (selection bias)	Low risk	Comment: Not described but probably done.
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Patients and study personnel were blind to treatment assign- ment. All patients received four oral tablets (drug or placebo) each day and an injection (drug or placebo) every 2 weeks. The staff administering injections were not part of the study team and provided no clinical ratings."
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "Symptom severity was assessed using the 30-item Positive and Negative Syndrome Scale (PANSS [9]), the PANSS-derived BPRS, and the Clinical Global Impressions-Severity of Illness (CGI-S [8]). Efficacy assessments were performed weekly for the first 12 weeks and every 2 weeks thereafter."
Incomplete outcome data (attrition bias)	Unclear risk	Quote: "All analyses were performed on an intent-to-treat basis" Quote: "(Patient flow through the study is shown in the data supplement accompanying the online version of this article.)" Comment: Dropouts described in additional file??
Selective reporting (reporting bias)	Low risk	no
Other bias	Low risk	no

Keks 2007

Methods	**Study design:** **Study grouping:** **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** Risperidone LAI ● *Age, mean (SD), y*: ● *Gender, % male*: ● *Age at first hospitalization, mean (SD), y*: SGA physician's choice ● *Age, mean (SD), y*: ● *Gender, % male*: ● *Age at first hospitalization, mean (SD), y*: **Included criteria:** **Excluded criteria:**
Interventions	**Intervention Characteristics** Risperidone LAI ● *Study duration*: ● *Dose*: SGA physician's choice ● *Study duration*:

	● *Dose*:
Outcomes	*Dichotomous*: ● Discontinuation due to adverse events ● Hospitalization within study duration ● Adverse events ● All-cause discontinuation ● Relapse, longest time-point ● Mortality
Identification	**Sponsorship source:** **Country:** **Setting:** **Comments:** **Authors name:** **Institution:** **Email:** **Address:**
Notes	**Identification:** **Participants:** **Study design:** **Baseline characteristics:** **Intervention characteristics:** **Pretreatment:** **Continuous outcomes:** **Dichotomous outcomes:** **Adverse outcomes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomised controlled week, open-label, randomised controlled international study" Quote: "Randomisation numbers were probabilities. Randomisation numbers were allocated by an interactive voice response allocated by an interactive voice response system (IVRS)."
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation numbers were probabilities. Randomisation numbers were allocated by an interactive voice response allocated by an interactive voice response system (IVRS). When a participant was system (IVRS). When a participant was ready to be randomised, the investigator ready to be randomised, the investigator called the IVRS by telephone and entered called the IVRS by telephone and entered the person's stratification information. the person's stratification information." Comment: Probably difficult to foresee or influence
Blinding of participants and personnel (performance bias)	High risk	Quote: "Randomised, controlled, open-label study"
Blinding of outcome assessment (detection bias)	High risk	Comment: Not described. I does not in general seem as tough efforts have been done to blind assessors - or personnel in general.
Incomplete outcome data (attrition bias)	Unclear risk	Quote: "Assessments were completed at baseline (randomisation), weeks 5, 9, 13, 25, 37 and (randomisation), weeks 5, 9, 13, 25, 37 and 53 and at end-point (last observation car- 53 and at end-point (last observation car- ried forward, LOCF)." Comment: 35 % and 38 % dropout respectively. Relatively large but not skewed..
Selective reporting (reporting bias)	Low risk	Quote: "NCT00236457) http://clinicaltrials.gov" Comment: Outcome from protocol reported
Other bias	Unclear risk	Quote: "The study was supported by Johnson & Johnson Pharmaceutical Research and Development. The Pharmaceutical Research and Development. The authors thank Ilse Van Hove, MSc (Johnson & John- authors thank Ilse Van Hove, MSc (Johnson & John- son Pharmaceutical Research and Development, son Pharmaceutical Research and Development, Beerse, Belgium) for completing the statistical ana- Beerse, Belgium) for completing the statistical ana- lyses." Comment: Ligefrem analyserne!

Li 1996

Methods	open 52 weeks N=320
Participants	—Schizophrenia CCMD-2 —37.2
Interventions	1.Haloperidol i.m. (range 100 – 150 mg 4-weekly) 2. Other oral antipsychotics (dose n.i.)
Outcomes	
Identification	

Notes	The allocation of 28 participants who dropped out is unclear

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	cf. Leucht 2011
Allocation concealment (selection bias)	Unclear risk	cf. Leucht 2011
Blinding of participants and personnel (performance bias)	Unclear risk	cf. Leucht 2011
Blinding of outcome assessment (detection bias)	Unclear risk	cf. Leucht 2011
Incomplete outcome data (attrition bias)	Unclear risk	cf. Leucht 2011
Selective reporting (reporting bias)	Low risk	cf. Leucht 2011
Other bias	Unclear risk	cf. Leucht 2011

MacFadden 2010

Methods	104 weeks N=355
Participants	Pts with sch who experienced at least 2 psychotic relapses in the past 2 years, and have been stabilised for >=2 months
Interventions	RIS LAI ARI
Outcomes	
Identification	
Notes	relapse: worsening of psychiatric symptoms, increase >25% PANSS T, self-injury, drug discontinuation

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Subjects were randomly assigned in a 1:1 ratio"
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias)	High risk	Quote: "open-label,"
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Relapse was determined by a five- member RMB blinded to subject treatment;"
Incomplete outcome data (attrition bias)	Low risk	Quote: "The efficacy analyses were based on the intent-to-treat (ITT) analysis set, which included all subjects randomly assigned to a treatment group who had received at least one dose of study drug and at least one postbaseline PANSS measurement." Quote: "Of the 409 subjects screened, 355 were randomly selected to receive study drug and 349 were included in the ITT analysis set." Comment: Relatively small amount of dropout after two years. Dropout not skewed.
Selective reporting (reporting bias)	Low risk	Quote: "(NCT00299702)" Comment: Outcomes from protocol reported
Other bias	Unclear risk	Comment: Kan dette have påvirket grupperne skævt? Quote: "The biweekly visits and regular assessments with numerous time- intensive scales increased interactions with treatment teams and may have enhanced nonspecific psychotherapeutic effects and increased adherence to oral treatment."

Malla 2013

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Open Label:** YES **Cluster RCT:**
Participants	**Baseline Characteristics** Risperidone LAI ● *Age, mean (SD), y*: 22.5 (3.12) ● *Gender, % male*: 78.6 ● *Age at first hospitalization, mean (SD), y*: SGA physician's choice ● *Age, mean (SD), y*: 23 (2.93) ● *Gender, % male*: 91.4 ● *Age at first hospitalization, mean (SD), y*: **Included criteria:** between 18 and 30 years of age; had a PANSS total score between 60 and120 at screening; and received a DSM-IV TR diagnosis for schizophrenia,schizophreniform or schizoaffective disorder based on the Structured

	Clinical Interviewfor DSM-IV (SCID-IV) no longer than 3 years prior to study entry.. In addition, femaleswere required to be surgically sterile or engaging in effective birth control methods. **Excluded criteria:** primary axis-I diagnosis was not within SSDSM-IV TR categories; if they were receiving mood stabilizers or antidepressants at thetime of entering the study; displayed current drug or alcohol dependence; were treatedwith depot antipsychotics within 3 months of study entry; had or were suspected of ahistory of hypersensitivity or allergy to risperidone; were risperidone non-responders;failed to respond to 2 or more adequate treatment trials of antipsychotics; had a clinicallysignificant laboratory abnormality or a serious unstable and untreated medical illness;were at significant risk of suicide or violence at study entry; required electroconvulsivetreatment within 3 months of study entry; received or used an experimental drug ordevice within 30 days before study entry; had previous treatment with clozapine; or ifthey were in a conflict of interest with the investigation
Interventions	**Intervention Characteristics** Risperidone LAI ● *Study duration*: The study began with an 18 week stabilization phase which was followed by an86 week maintenance phase for both arms. ● *Dose*: 31.75 mg (8.82)/2 weeks SGA physician's choice ● *Study duration*: The study began with an 18 week stabilization phase which was followed by an86 week maintenance phase for both arms. ● *Dose*: 10 participants received olanazapine; 2 quetiapine, and 20risperidone. During the maintenance phase mean doseswere 15.5mg for olanzapine (SD =5.39; median: 17.5; mode: 14.60; range: 15-20mg),400mg for quetiapine (SD =141.42; median: 400; mode: 400; range: 400-500mg) and3.82mg for risperidone (SD =1.87; median: 3.9; mode: 3.2; range: 1-6mg).
Outcomes	*Dichotomous*: ● Discontinuation due to adverse events ● Hospitalization within study duration ● Adverse events ● All-cause discontinuation ● Relapse, longest time-point: psychiatric hospitalization, needed an increase in psychiatric care and experienced a significant increase in PANSS scores; demonstrated much worse on the CGI-S; deliberate self-injury; suicidal or homicidal indeation; violent behaviour ● Mortality
Identification	**Sponsorship source:** This study was sponsored and funded by Janssen Canada **Country:** Canada **Setting:** outpatient/inpatient setting not described **Comments:** **Authors name:** Ashok Malla **Institution:** Department of Psychiatry, McGill University, Montreal, Quebec **Email:** **Address:**
Notes	**Identification:** **Participants:** **Study design:** **Baseline characteristics:** **Intervention characteristics:** **Pretreatment:** **Continuous outcomes:** **Dichotomous outcomes:** *Louise Klokker Madsen* Adverse event in table= weight gain (>7%)Discont. due to adverse events for both groups: Reasons for dropout among those who reachedstabilization included adverse events (n = 3)Reasons for dropout among participants who had not stabilizedincluded adverse events (n = 2);Reasons for hospitalization includedexacerbation of symptoms, relapse, or adverse events. The latter included alcoholdependence syndrome (n =1), a depressive state marked by suicidal ideation (n = 1) inparticipants receiving RLAI, and lacerations to the face (n = 1), nausea andthrombocytopenia (n = 1) for those receiving oral SGAs. **Adverse outcomes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Eligible patients were randomly assigned to one of two treatment conditions." Comment: Randomized, not further described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias)	High risk	Comment: Open-label study
Blinding of outcome assessment (detection bias)	High risk	Comment: Open-label study
Incomplete outcome data (attrition bias)	High risk	Comment: > 50% dropout from the maintenance phase
Selective reporting (reporting bias)	Low risk	Comment: No evidence of selective reporting
Other bias	Low risk	Comment: No other obvious source of bias

NCT00246259

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clear how randomization was done
Allocation concealment (selection bias)	High risk	
Blinding of participants and personnel (performance bias)	High risk	
Blinding of outcome assessment (detection bias)	High risk	not described. It does not in general seem as though efforts were doneto blind assessors.
Incomplete outcome data (attrition bias)	Unclear risk	not clear
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Potapov 2008

Methods	Open 52 weeks N=20
Participants	—Schizophrenia, PANSS>60 —34.9
Interventions	1. Risperidone i.m. (41.7± 10.6 mg biweekly) 2. Oral olanzapine (15.9± 5,0 mg daily)
Outcomes	
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	cf. Leucht 2011
Allocation concealment (selection bias)	Low risk	cf. Leucht 2011
Blinding of participants and personnel (performance bias)	High risk	cf. Leucht 2011
Blinding of outcome assessment (detection bias)	High risk	cf. Leucht 2011
Incomplete outcome data (attrition bias)	Low risk	cf. Leucht 2011
Selective reporting (reporting bias)	High risk	cf. Leucht 2011
Other bias	Low risk	cf. Leucht 2011

Rosenheck 2011

Methods	**Study design:** **Study grouping:** **Open Label:** **Cluster RCT:**
Participants	**Baseline Characteristics** Risperidone LAI ● *Age, mean (SD), y*: ● *Gender, % male*: ● *Age at first hospitalization, mean (SD), y*: SGA physician's choice ● *Age, mean (SD), y*: ● *Gender, % male*: ● *Age at first hospitalization, mean (SD), y*: **Included criteria:**

	Excluded criteria:
Interventions	**Intervention Characteristics** Risperidone LAI ● *Study duration*: ● *Dose*: SGA physician's choice ● *Study duration*: ● *Dose*:
Outcomes	*Dichotomous*: ● Discontinuation due to adverse events ● Hospitalization within study duration ● Adverse events ● All-cause discontinuation ● Relapse, longest time-point ● Mortality
Identification	**Sponsorship source:** **Country:** **Setting:** **Comments:** **Authors name:** **Institution:** **Email:** **Address:**
Notes	**Identification:** **Participants:** **Study design:** **Baseline characteristics:** **Intervention characteristics:** **Pretreatment:** **Continuous outcomes:** **Dichotomous outcomes:** **Adverse outcomes:**

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was conducted centrally and strat- ified according to site because of potential prac- tice differences. Randomization was conducted with the use of randomly permuted blocks of variable size to ensure an approximate balance over time."
Allocation concealment (selection bias)	Unclear risk	no info
Blinding of participants and personnel (performance bias)	High risk	Comment: Not possible t blind patients or treating personnel
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Blinded videoconference assessments were com- pleted every 3 months on measures of symptoms, quality of life, and functioning."
Incomplete outcome data (attrition bias)	Low risk	Comment: 10 dropouts in oral group, 3 in injection group. ITT analysis and relatively small and not too skewed dropuout.
Selective reporting (reporting bias)	Low risk	Comment: Outcomes described in protocol. outcomes seem relevant compared with other studies.
Other bias	Low risk	

Schooler 1979

Methods	—db (double dummy) —Four centres 52 weeks N=214
Participants	—Schizophrenia, DSM-II, at least moderately ill on at least one BPRS positive symptom —29 years
Interventions	1. Fluphenazine decanoate+ oral PBO (mean 34.2 mg/i.m. 3 weekly, range 12.5–100 mg/im, n= 107) 2. Fluphenazine hydrochloride+ i.m. PBO (mean 24.8 mg daily, range 2.5–60 mg daily, n= 107)
Outcomes	

Identification	
Notes	—Patients who failed to attend visits were contacted by telephone or home visits —Randomisation occurred in the acute phase

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	cf. Leucht 2011
Allocation concealment (selection bias)	Unclear risk	cf. Leucht 2011
Blinding of participants and personnel (performance bias)	Low risk	cf. Leucht 2011
Blinding of outcome assessment (detection bias)	Low risk	cf. Leucht 2011
Incomplete outcome data (attrition bias)	Low risk	cf. Leucht 2011
Selective reporting (reporting bias)	High risk	cf. Leucht 2011
Other bias	High risk	cf. Leucht 2011

Footnotes

Characteristics of excluded studies

Detke 2011

Reason for exclusion	this conference abstract of the study is excluded and the full report (Detke 2014) included instead

Kamijima 2009

Reason for exclusion	Article written in Japanese, not possible to asses risk of bias, even though data were extracted in Kishimoto 2014

Kaneno 1991

Reason for exclusion	Article written in Japanese, not possible to asses risk of bias, even though data were extracted in Kishimoto 2014

Rifkin 1977

Reason for exclusion	Patients were required to be in stable remission to be included

Schooler 2011

Reason for exclusion	this conference abstract is excluded and instead the full report of this study (Buckley 2014) has been included

Stargardt 2008

Reason for exclusion	Wrong intervention

Strom 2011

Reason for exclusion	Wrong intervention

Ward 2006

Reason for exclusion	Wrong intervention

Yu 2009

Reason for exclusion	Wrong intervention

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

References to studies

Included studies

Arango 2006

[Empty]

Bai 2007

Bai,Y. M.; Ting Chen,T.; Chen,J. Y.; Chang,W. H.; Wu,B.; Hung,C. H.; Kuo Lin,W.. Equivalent switching dose from oral risperidone to risperidone long-acting injection: a 48-week randomized, prospective, single-blind pharmacokinetic study. The Journal of clinical psychiatry 2007;68(8):1218-1225. [DOI:]

Barnes 1983

[Empty]

Buckley 2014

Buckley,P. F.; Schooler,N. R.; Goff,D. C.; Hsiao,J.; Kopelowicz,A.; Lauriello,J.; Manschreck,T.; Mendelowitz,A. J.; Miller,D. D.; Severe,J. B.; Wilson,D. R.; Ames,D.; Bustillo,J.; Mintz,J.; Kane,J. M.; the PROACTIVE Study. Comparison of SGA Oral Medications and a Long-Acting Injectable SGA: The PROACTIVE Study. Schizophrenia bulletin 2014;(Journal Article). [DOI: sbu067 [pii]]

Crawford 1974

Crawford, R.; Forrest, A.. Controlled trial of depot fluphenazine in out-patient schizophrenics. British Journal of Psychiatry 1974;124(0):385-91. [DOI:]

Del Guidice 1975

[Empty]

Detke 2014

[Empty]

Fallon 1978

[Empty]

Fleischhacker 2014

[Empty]

Gaebel 2010

[Empty]

Glick 2005

Glick,I. D.; Marder,S. R.. Long-term maintenance therapy with quetiapine versus haloperidol decanoate in patients with schizophrenia or schizoaffective disorder. The Journal of clinical psychiatry 2005;66(5):638-641. [DOI:]

Hogarty 1979

[Empty]

Kane 2010

Kane, J. M.; Detke, H. C.; Naber, D.; Sethuraman, G.; Lin, D. Y.; Bergstrom, R. F.; McDonnell, D.. Olanzapine long-acting injection: a 24-week, randomized, double-blind trial of maintenance treatment in patients with schizophrenia. American journal of psychiatry 2010;167(2):181-189. [DOI: 10.1176/appi.ajp.2009.07081221 [doi]]

Keks 2007

Keks, N. A.; Ingham, M.; Khan, A.; Karcher, K.. Long-acting injectable risperidone v. olanzapine tablets for schizophrenia or schizoaffective disorder: Randomised, controlled, open-label study. British Journal of Psychiatry 2007;191(AUG.):131-139. [DOI: 191/2/131 [pii]]

Li 1996

[Empty]

MacFadden 2010

[Empty]

Malla 2013

Malla,A.; Chue,P.; Jordan,G.; Stip,E.; Koczerginski,D.; Milliken,H.; Joseph,A.; Williams,R.; Adams,B.; Manchanda,R.; Oyewumi,K.; Roy,M. A.. An Exploratory Open-Label Randomized Trial Comparing Risperidone Long Acting Injectable (RLAI) with Oral Antipsychotic Medication in the Treatment of Early Psychosis. Clinical schizophrenia & related psychoses 2013;(Journal Article):1-26. [DOI: V0T7554T54H67185 [pii]]

NCT00246259

[Empty]

Potapov 2008

[Empty]

Rosenheck 2011

Rosenheck,R. A.; Krystal,J. H.; Lew,R.; Barnett,P. G.; Fiore,L.; Valley,D.; Thwin,S. S.; Vertrees,J. E.; Liang,M. H.; CSP555 Research,Group. Long-acting risperidone and oral antipsychotics in unstable schizophrenia. New England Journal of Medicine 2011;364(9):842-851. [DOI: 10.1056/NEJMoa1005987 [doi]]

Schooler 1979

[Empty]

Excluded studies

Detke 2011

Detke, H. C.; Weiden, P. J.; Llorca, P. M.; Choukour, M.; Watson, S. B.; Brunner, E.; Ascher-Svanum, H.. Open-label comparison of olanzapine long-acting injection and oral olanzapine: A 2-year, randomized study in outpatients with schizophrenia. Schizophrenia bulletin 2011;37(Suppl. 1):300. [DOI:]

Kamijima 2009

[Empty]

Kaneno 1991

[Empty]

Rifkin 1977

[Empty]

Schooler 2011

Schooler,N. R.; Buckley,P. F.; Mintz,J.; Goff,D. C.; Kopelowicz,A.; Lauriello,J.; Manschreck,T.; Mendelowitz,A. J.; Miller,D. D.; Wilson,D. R.; Bustillo,J.; Severe,J. B.; Kane,J. M.. PROACTIVE: Initial results of an RCT comparing long-acting injectable risperidone to 2nd generation oral antipsychotics.. Neuropsychopharmacology 2011;36(Journal Article):S104-S105. [DOI:]

Stargardt 2008

Stargardt,T.; Weinbrenner,S.; Busse,R.; Juckel,G.; Gericke,C. A.. Effectiveness and cost of atypical versus typical antipsychotic treatment for schizophrenia in routine care. The journal of mental health policy and economics 2008;11(2):89-97. [DOI:]

Strom 2011

Strom, B. L.; Eng, S. M.; Faich, G.; Reynolds, R. F.; D'Agostino, R. B.; Ruskin, J.; Kane, J. M.. Comparative mortality associated with ziprasidone and olanzapine in real-world use among 18,154 patients with schizophrenia: The Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC). Am J Psychiatry 2011;168(2):193-201. [DOI: 10.1176/appi.ajp.2010.08040484 [doi]]

Ward 2006

Ward, A.; Ishak, K.; Proskorovsky, I.; Caro, J.. Compliance with refilling prescriptions for atypical antipsychotic agents and its association with the risks for hospitalization, suicide, and death in patients with schizophrenia in Quebec and Saskatchewan: a retrospective database study. Clinical Therapeutics 2006;28(11):1912-21. [DOI: S0149-2918(06)00272-4 [pii]]

Yu 2009

Yu,A. P.; Atanasov,P.; Ben-Hamadi,R.; Birnbaum,H.; Stensland,M. D.; Philips,G.. Resource utilization and costs of schizophrenia patients treated with olanzapine versus quetiapine in a Medicaid population. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 2009;12(5):708-715. [DOI: 10.1111/j.1524-4733.2008.00498.x [doi]]

Data and analyses

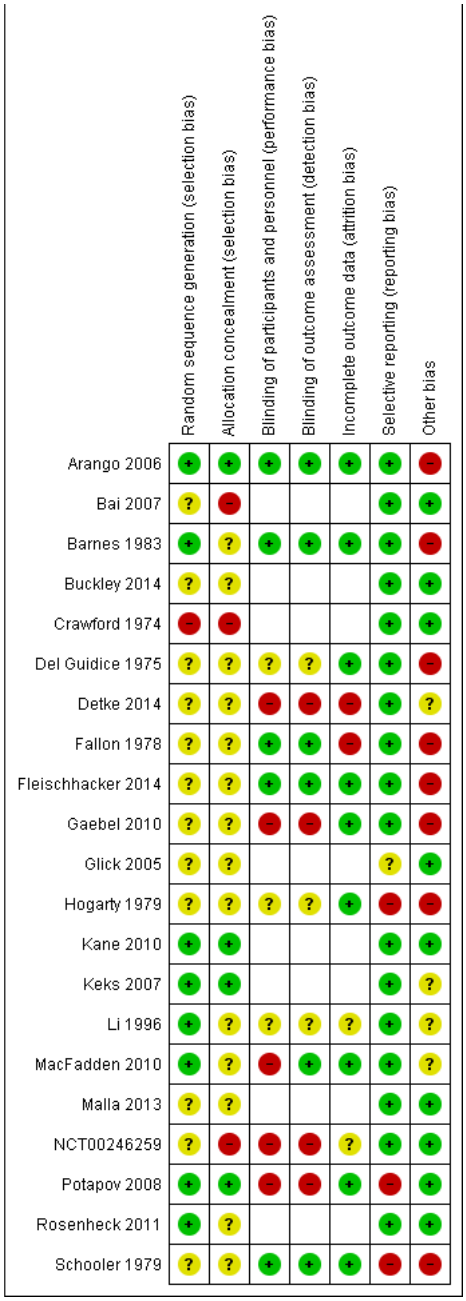
1 Depot AP versus oral AP

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Relapse, longest FU	21	5329	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.79, 1.10]
1.1.1 Fluphenazine depot	6	516	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.62, 1.00]
1.1.2 Haloperidol depot	2	317	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.38, 1.20]
1.1.3 Olanzapine LAI	2	1445	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.89, 1.56]
1.1.4 Risperidone LAI	9	2474	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.77, 1.36]
1.1.5 Zuclopenthixol depot	1	46	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.56, 2.93]
1.1.6 Aripiprazole LAI	1	531	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.59, 1.87]
1.2 All-cause discontinuation, longest FU	19	4978	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.87, 1.08]
1.2.1 Fluphenazine depot	5	411	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.73, 1.10]
1.2.2 Haloperidol depot	1	29	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.39, 1.61]
1.2.3 Olanzapine LAI	2	1445	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.86, 1.80]
1.2.4 Risperidone LAI	9	2516	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.83, 1.06]
1.2.5 Zuclopenthixol depot	1	46	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.09, 2.78]
1.2.6 Ariprazole LAI	1	531	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.60, 1.03]
1.3 Hospitalization (at least 1 hospitalization within study duration), longest FU	10	2390	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.70, 1.08]
1.3.1 Fluphenazine depot	4	197	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.67, 0.99]
1.3.2 Olanzapine LAI	1	524	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.46, 1.45]
1.3.3 Risperidone LAI	3	1331	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.61, 1.30]

1.3.4 Zuclopenthixol depot	1	46	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.56, 2.93]
1.3.5 Haloperidol depot	1	292	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.05, 1.02]
1.4 Mortality. longest FU	8	4302	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.28, 1.30]
1.5 Quality of life, longest FU	2	906	Std. Mean Difference (IV, Random, 95% CI)	0.64 [-0.72, 1.99]
1.5.1 Heinrichs-Carpenter Quality of Life Scale (QLS)	2	906	Std. Mean Difference (IV, Random, 95% CI)	0.64 [-0.72, 1.99]
1.6 Discontinuation due to adverse events, longest FU	18	4749	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.78, 1.45]
1.6.1 Fluphenazine depot	6	516	Risk Ratio (M-H, Random, 95% CI)	1.61 [0.53, 4.92]
1.6.2 Aripiprazole	1	531	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.42, 3.12]
1.6.3 Olanzapine LAI	2	1445	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.73, 1.74]
1.6.4 Risperidone LAI	8	2211	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.45, 1.89]
1.6.5 Zuclopenthixol depot	1	46	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.7 Injection site adverse events, longest FU	2	1055	Risk Ratio (M-H, Random, 95% CI)	7.80 [0.68, 89.73]
1.7.1 Olanzapine LAI	1	524	Risk Ratio (M-H, Random, 95% CI)	34.47 [2.08, 570.24]
1.7.2 Aripipraozole LAI	1	531	Risk Ratio (M-H, Random, 95% CI)	3.35 [1.37, 8.20]
1.8 Number of violent episodes per month during the study, longest FU	1	46	Mean Difference (IV, Random, 95% CI)	-1.19 [-1.84, -0.54]

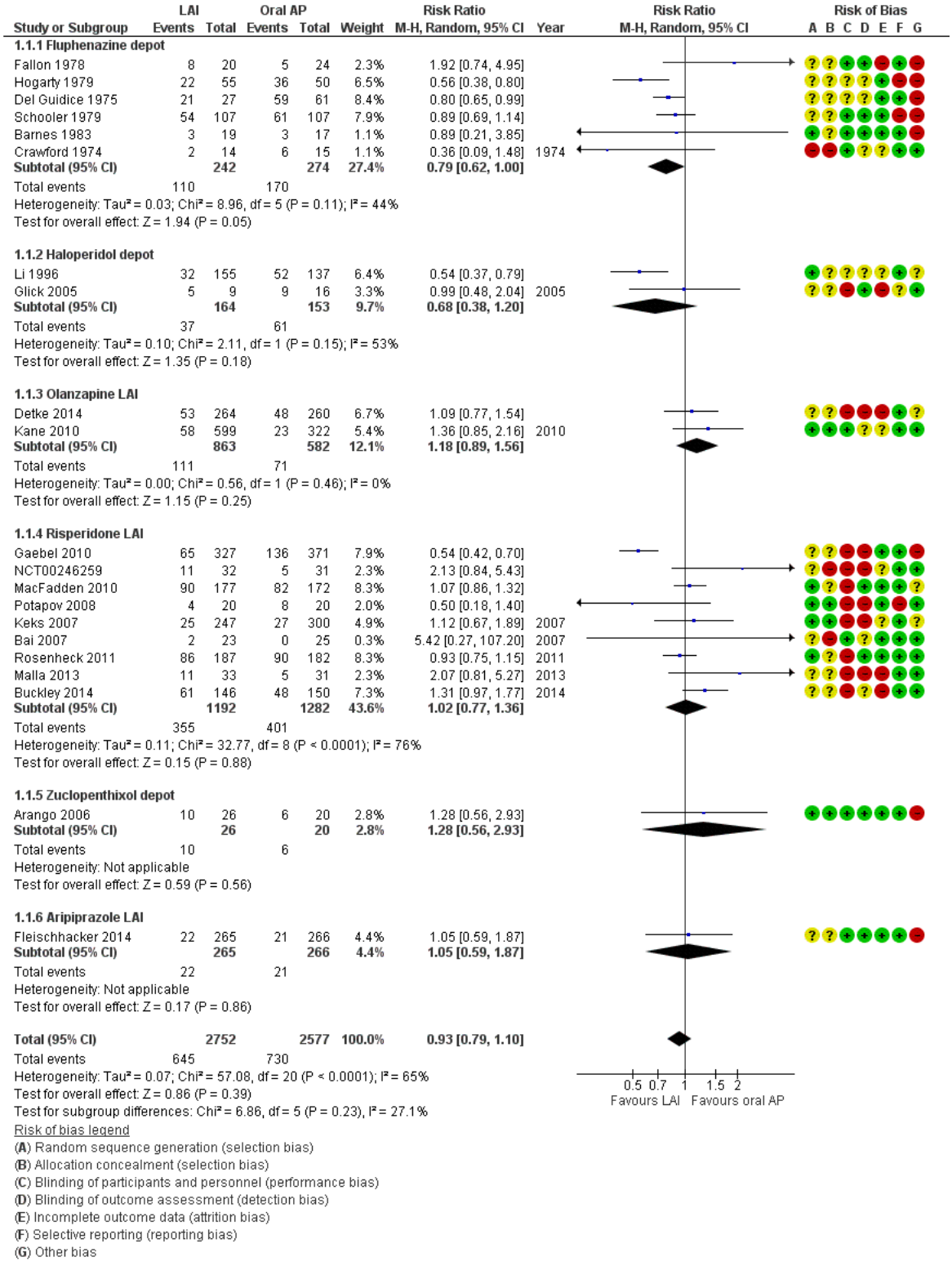
Figures

Figure 1



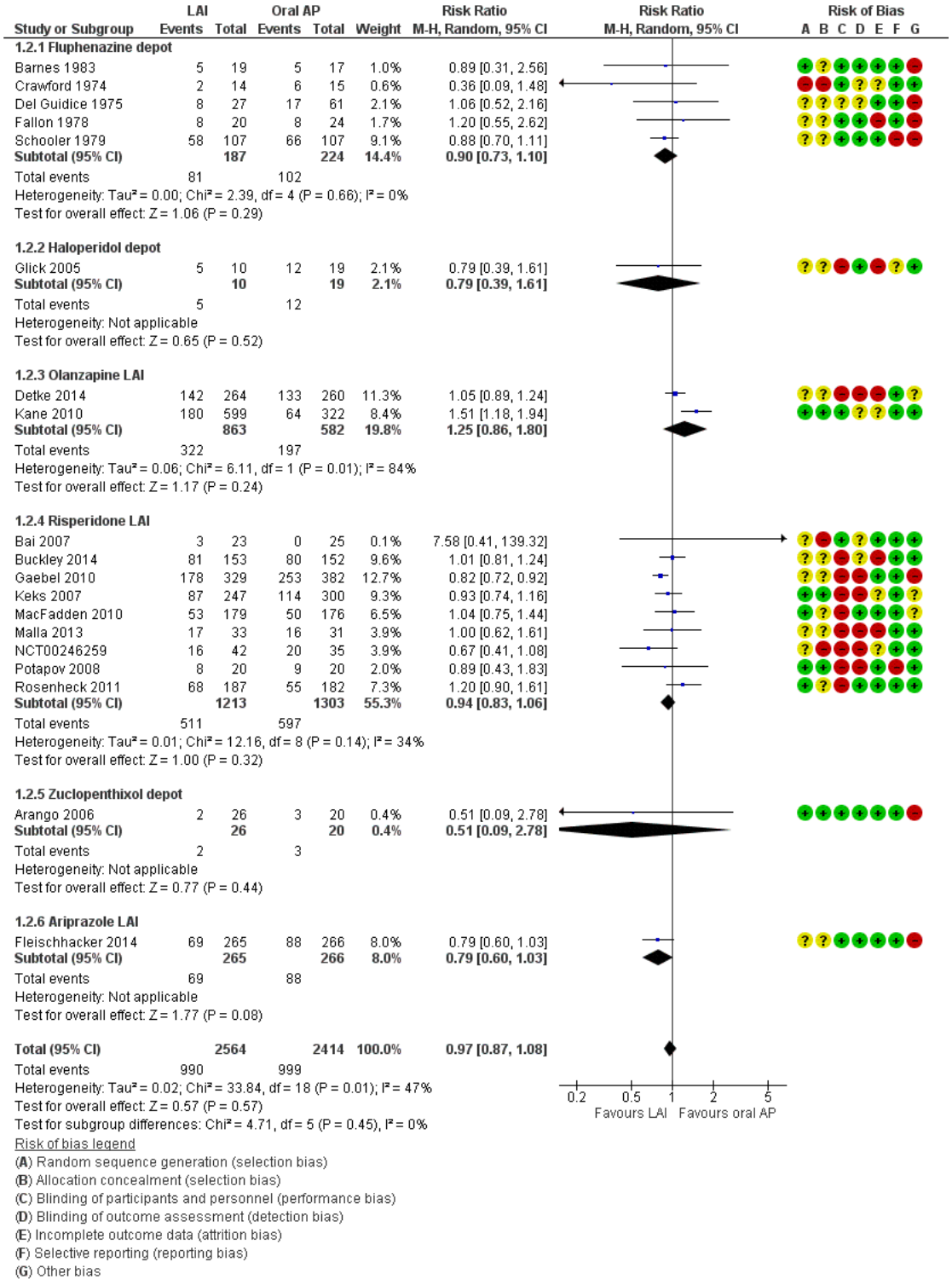
Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure 2 (Analysis 1.1)



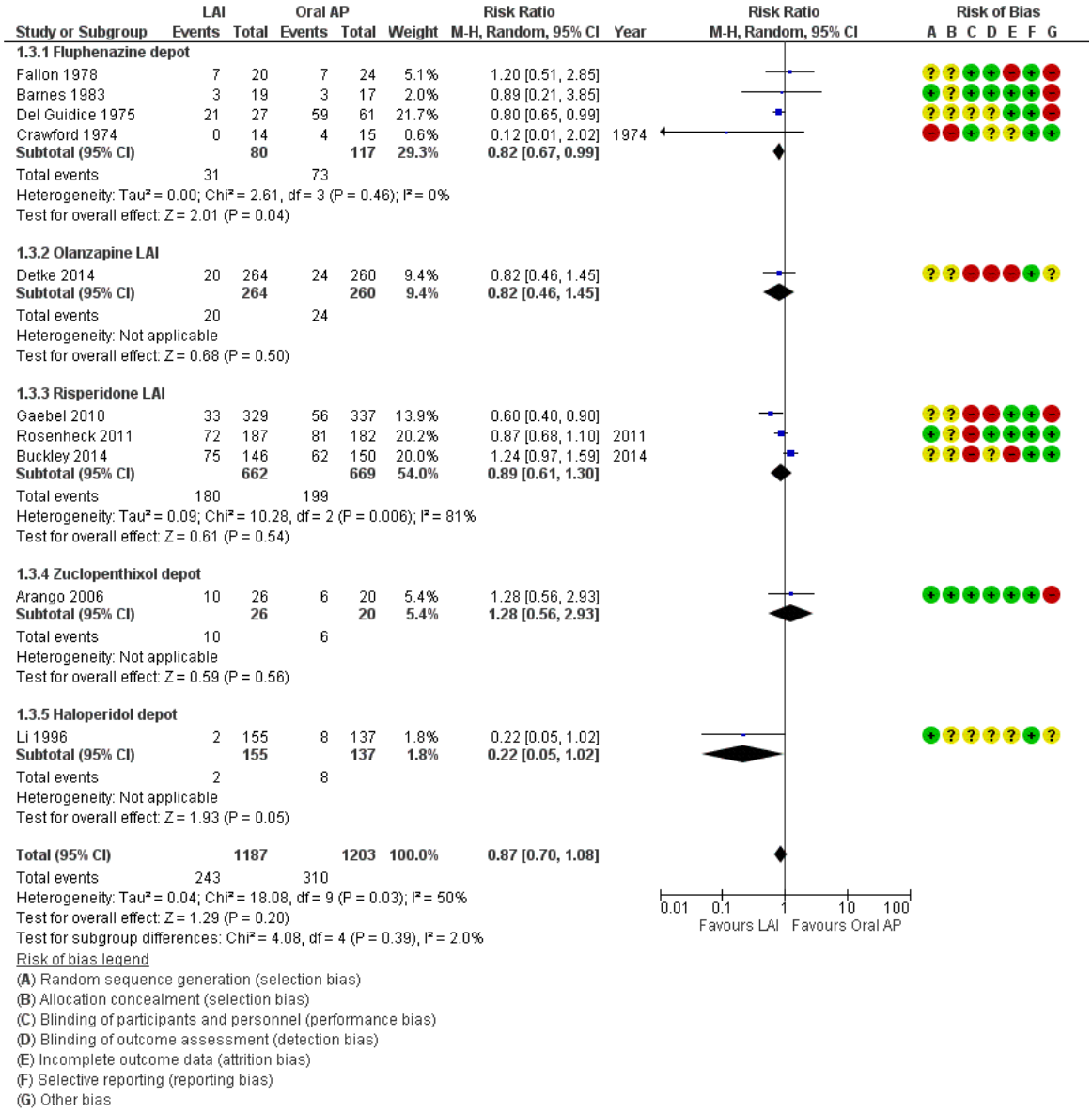
Forest plot of comparison: 3 Depot AP versus oral AP, outcome: 3.1 Relapse (longest time point).

Figure 3 (Analysis 1.2)



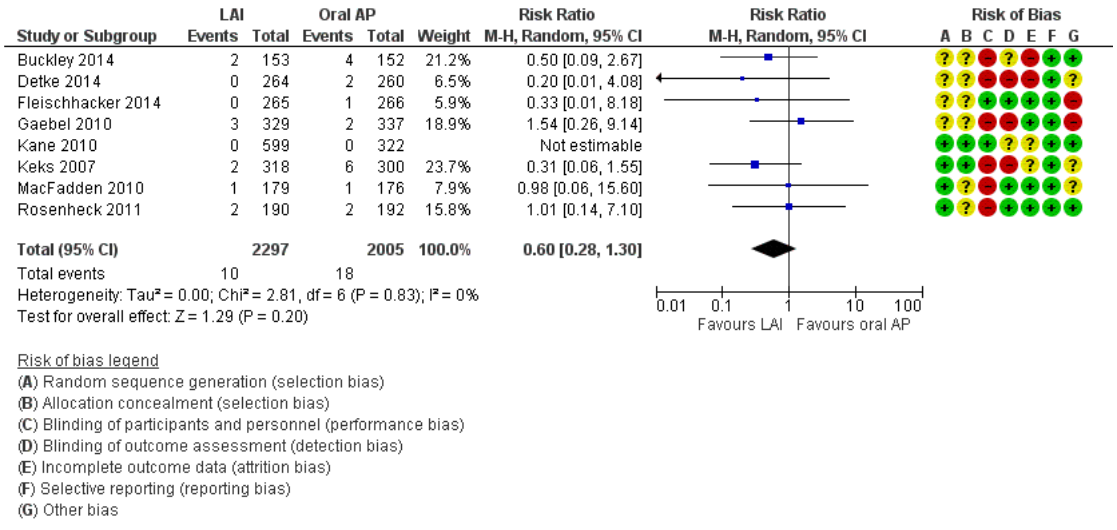
Forest plot of comparison: 1 Depot AP versus oral AP, outcome: 1.2 All-cause discontinuation, longest FU.

Figure 4 (Analysis 1.3)



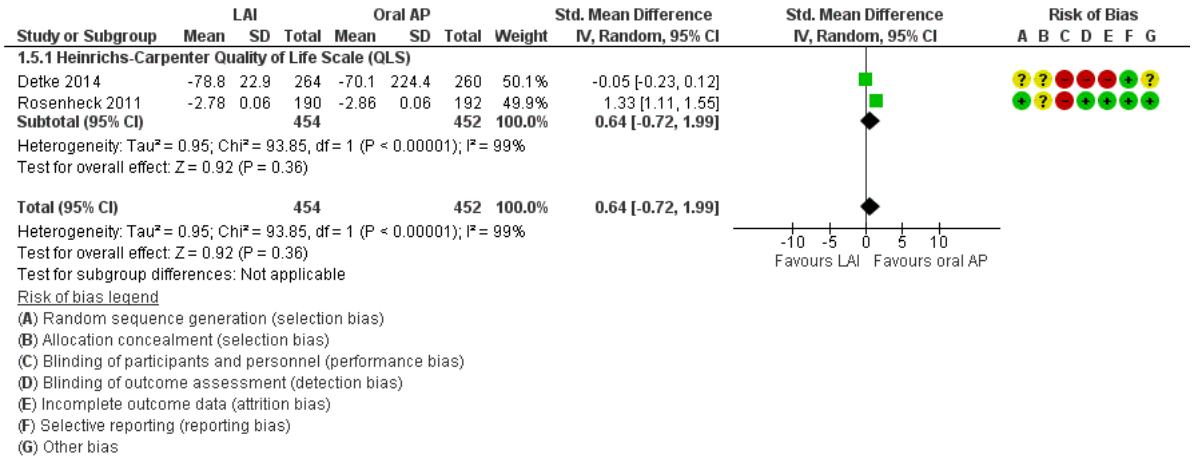
Forest plot of comparison: 1 Depot AP versus oral AP, outcome: 1.3 Hospitalization (at least 1 hospitalization within study duration), longest FU.

Figure 5 (Analysis 1.4)



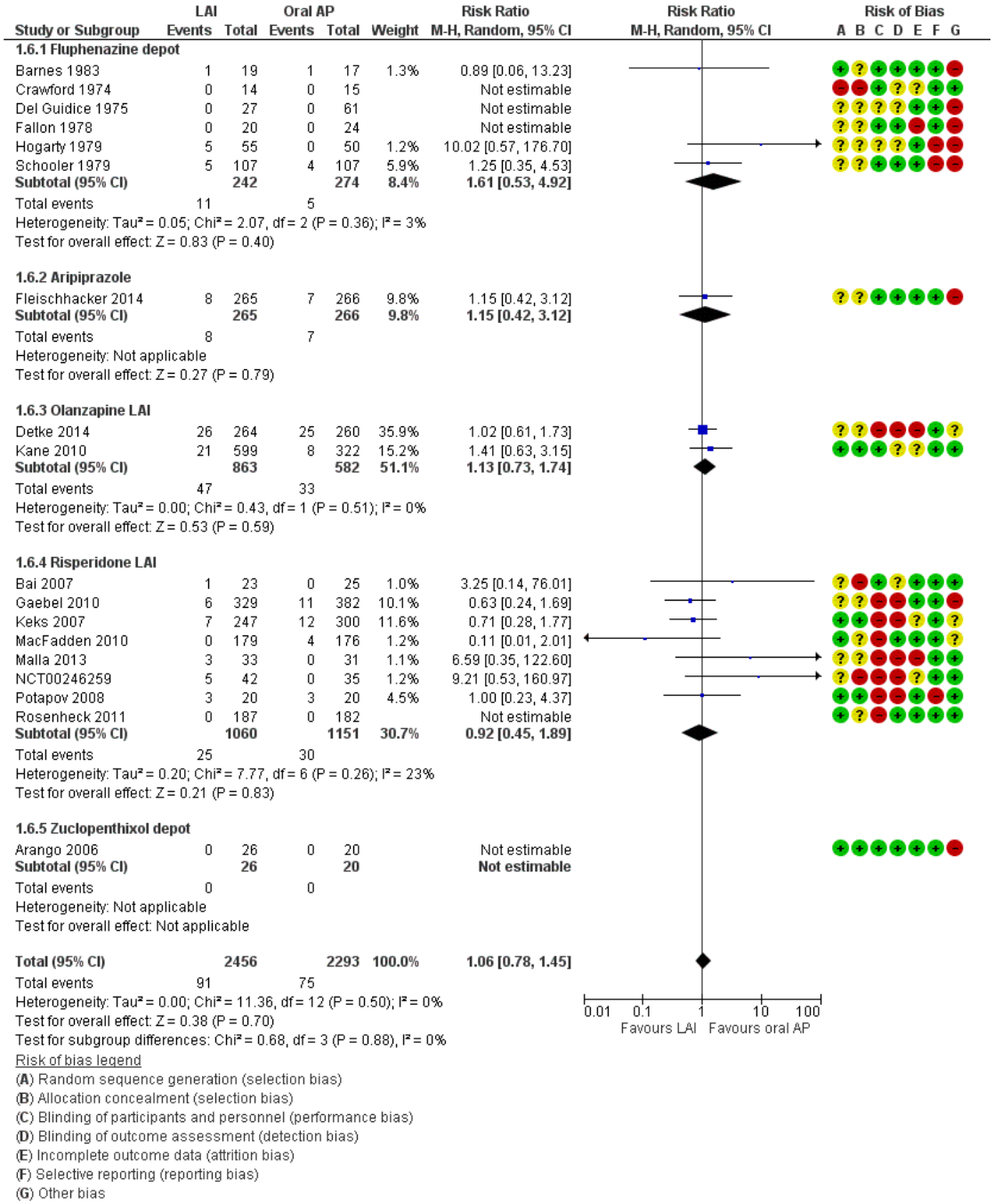
Forest plot of comparison: 1 Depot AP versus oral AP, outcome: 1.4 Mortality. longest FU.

Figure 6 (Analysis 1.5)



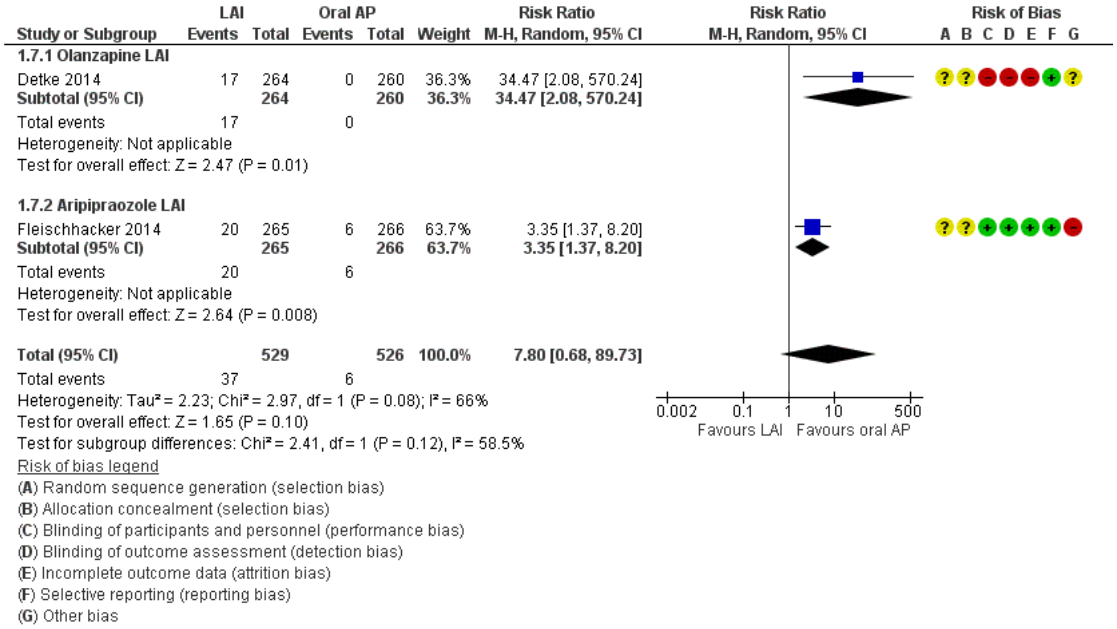
Forest plot of comparison: 1 Depot AP versus oral AP, outcome: 1.5 Quality of life, longest FU.

Figure 7 (Analysis 1.6)



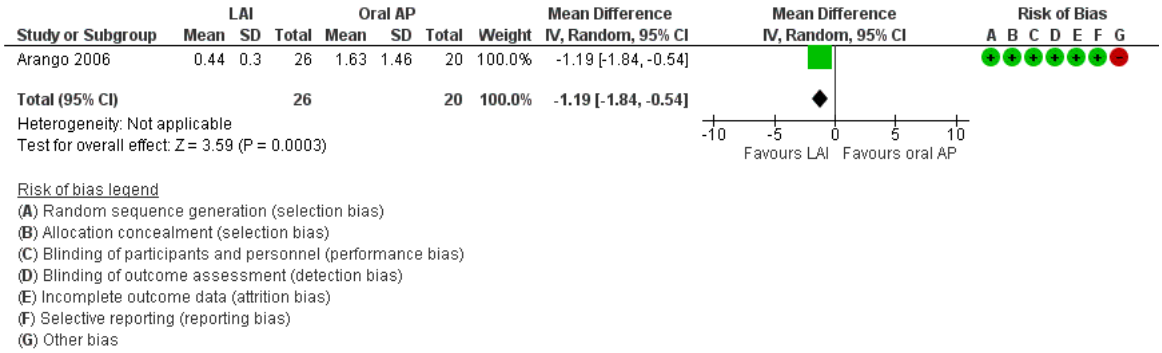
Forest plot of comparison: 1 Depot AP versus oral AP, outcome: 1.6 Discontinuation due to adverse events, longest FU.

Figure 8 (Analysis 1.7)



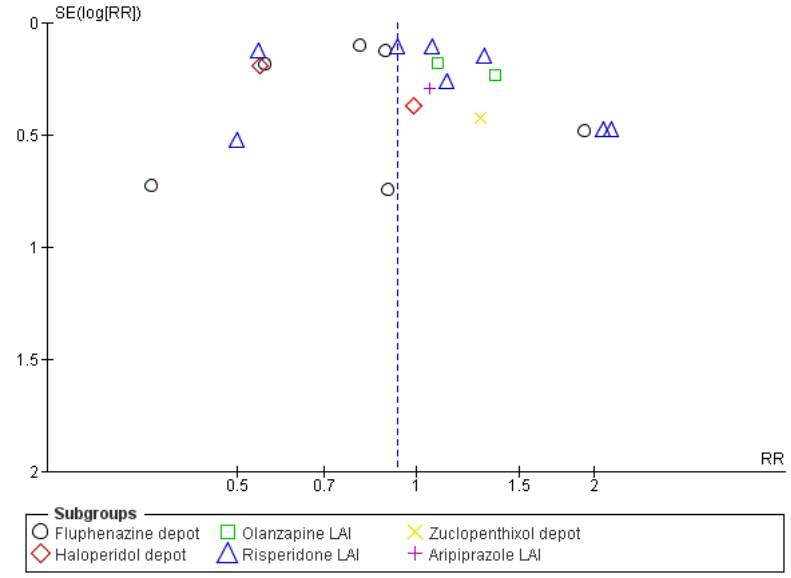
Forest plot of comparison: 1 Depot AP versus oral AP, outcome: 1.7 Injection site adverse events, longest FU.

Figure 9 (Analysis 1.8)



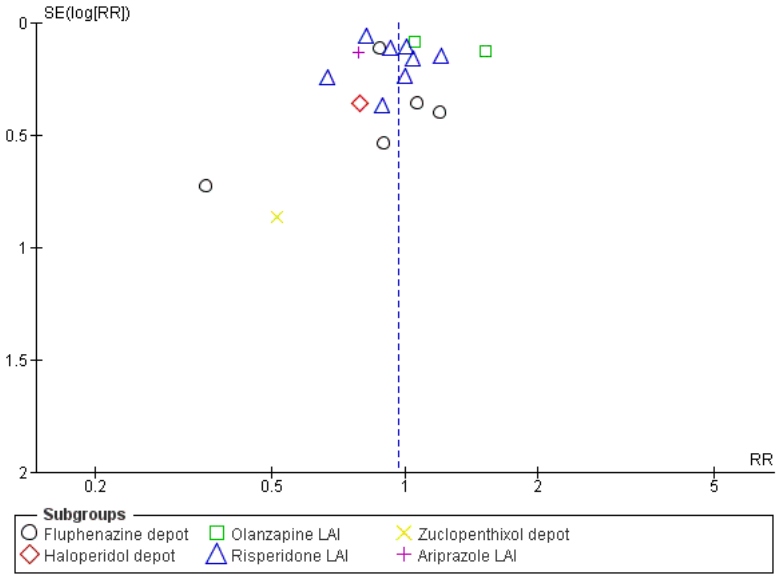
Forest plot of comparison: 1 Depot AP versus oral AP, outcome: 1.8 Number of violent episodes per month during the study, longest FU.

Figure 10 (Analysis 1.1)



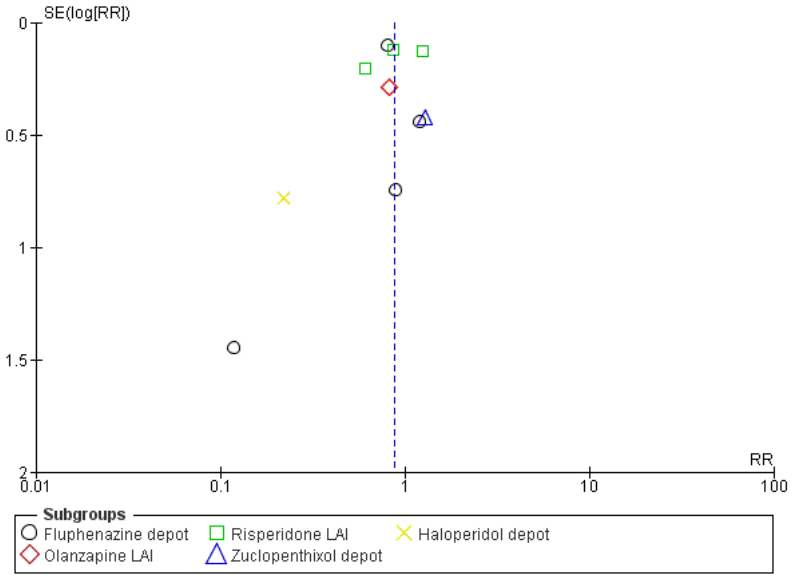
Funnel plot of comparison: 1 Depot AP versus oral AP, outcome: 1.1 Relapse, longest FU.

Figure 11 (Analysis 1.2)



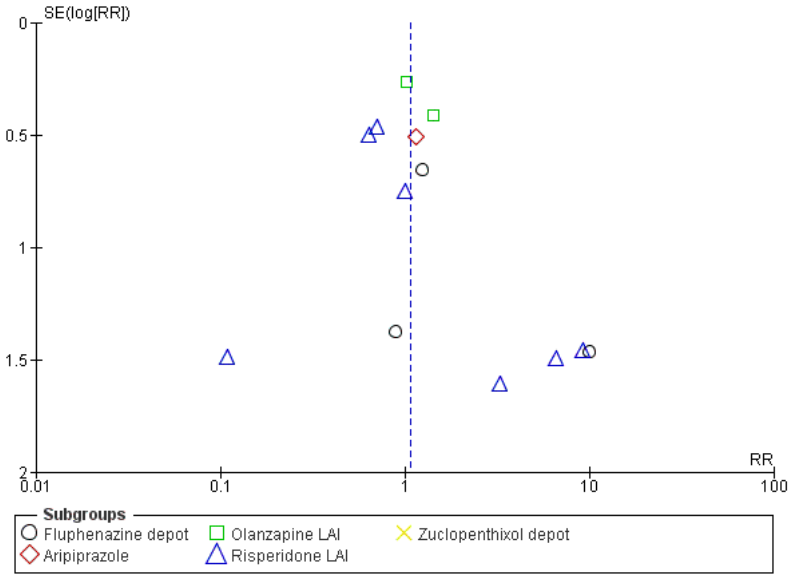
Funnel plot of comparison: 1 Depot AP versus oral AP, outcome: 1.2 All-cause discontinuation, longest FU.

Figure 12 (Analysis 1.3)



Funnel plot of comparison: 1 Depot AP versus oral AP, outcome: 1.3 Hospitalization (at least 1 hospitalization within study duration), longest FU.

Figure 13 (Analysis 1.6)



Funnel plot of comparison: 1 Depot AP versus oral AP, outcome: 1.6 Discontinuation due to adverse events, longest FU.