NKR24 - PICO4 - Schizophrenia: Maintenance treatment with APs versus discontinuation for non-remitted schizophrenia patients

Characteristics of studies

Characteristics of included studies

Andrews 1976

Methods	Randomisation: randomised, no further details. Allocation: pharmacists held the key. Blinding: double, identical capsules. Duration: 42 weeks. Design: parallel. Location: single-centre. Setting: hospital.
Participants	Diagnosis: schizophrenia (clinical diagnosis), continuously in hospital for at least 6 years (mean 28 years). N=32. Gender: 32 men. Age: mean 58 years. History: duration stable-8 weeks, duration ill NI- mean duration of hospitalisation 28 years, number of previous hospitalisations- n.i., age at onset- n.i., severity of illness-mean Wing Behaviour Scale Withdrawal Score 2.14, baseline antipsychotic dose-216mg/day CPZ equivalent
Interventions	1. Drug: Chlorpromazine - mean dose: 216mg/day. N=15. Allowed dose range: the participants were kept on their initial dose 2. Placebo: Duration of taper 0 days. N=17. Rescue medication: benzodiazepines, anticholinergics.
Outcomes	Examined: Relapse (need of antipsychotic medication). Leaving the study early. Unable to use / Not included: Behaviour: Ward Behaviour Rating Scale of Wing (no SD / no prespecified outcome of interest)
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, no further details.
Allocation concealment (selection bias)	Low risk	Pharmacists held the key.
Blinding of participants and personnel (performance bias)	Low risk	Double, identical capsules.
Blinding of outcome assessment (detection bias)	Low risk	Double, identical capsules.
Incomplete outcome data (attrition bias)	Low risk	All participants completed the trial.
Selective reporting (reporting bias)	Low risk	No evidence for selective reporting.
Other bias	Low risk	No obvious other bias.

Arato 2002

Methods	Randomisation: random, computer-generated randomisation code. Allocation: procedure not described. Blinding: double. Duration: 12 months. Design: parallel. Location: multi-centre. Setting: inpatient.
Participants	Diagnosis: chronic, stable schizophrenia (DSM-III-R), less than markedly ill on Clinical Global Impression Scale N=278. Gender: 203 men, 75 women. Age: mean 49.7 years. History: duration stable- n.i., duration ill- mean 21.8 years, number of previous hospitalisations- mean 10.1, age at onset- mean 27.9 years, severity of illness- mean PANSS 85.8, mean CGI severity 4.02, baseline antipsychotic dose n.i..
Interventions	1. Drug: ziprasidone - Fixed doses of 40, 80 or 160 mg/day.** N=207 2. Placebo: Duration of taper <3 days. N=71. Rescuemedication: anticholinergics, lorazepam, temazepam, no additional antipsychotic medication

Outcomes	Examined: Relapse: (Clinical Global Impressionof much worse or more, PANSS items hostility or uncooperativeness > 6, or in need for additional treatment for exacerbation of symptoms) Leaving the study early. Adverse events: binary outcome for generel, specific (movement disorders) - interviews Unable to use / Not included: Mental state: PANSS total score and subscores (no predefined outcome of interest) Global state: much worse or more - Clinical Global Impression Severity Scale (no prespecified outcome of interest) Functioning: Global Assessment of Functioning Scale (no prespecified outcome of interest) Adverse effects: extrapyramidal symptoms (SimpsonAngus Scale, Barnes Akathisia Scale, Abnormal Involuntary Movements Scale - all no SD / continous side-effect results were not among the prespecified outcomes of interest) Physiological measures: ECG, vital signs, weight, ophthalmological assessment, lab tests (all no SD, no data / not prespecified outcomes of interest)
Notes	** The results of the three dose groups were pooled. 16 participants from one centre were excluded due to protocol violations. Intention-to-treat were only those participants who had received at least one dose. How many did not receive one dose is unclear

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, computer-generated randomised code.
Allocation concealment (selection bias)	Unclear risk	Procedure not described.
Blinding of participants and personnel (performance bias)	Low risk	Double, no further details.
Blinding of outcome assessment (detection bias)	Low risk	Double, no further details.
Incomplete outcome data (attrition bias)	High risk	64%of the participants left the study early, most due to relapse. The rate was higher in the placebo group (86%) than in the medication group (~57%). This was probably not a problem for the primary outcome relapse, but for secondary outcomes for which the last-observation-carried-forward method was used. Appropriate survival curve analysis was used for the primary outcome relapse
Selective reporting (reporting bias)	Low risk	No selective reporting.
Other bias	Low risk	No obvious other bias.

Crow 1986

Methods	Randomisation: random, no further details. Allocation: allocation lists prepared by pharmacy for five antipsychotic drugs mentioned below, concealment is unclear. Blinding: double, no further details. Duration: 104 weeks. Design: parallel. Location: multi-centre. Setting: outpatient.
Participants	Diagnosis: first episode of schizophrenia (Present State Examination) N=120. Gender: 74 men, 46 women. Age: mean 26.3 years (range 16-59 years). History: duration stable- 30 days after discharge all on active medication, duration ill-2.8 months (between illness onset and admission to hospital), number of previous hospitalisations- n.i., age at onset- n.i., severity of illness- most participants were 'well' at the beginning of the study (91 well, 13 psychotic features, 10 defect state, 6 unspecific symptoms), baseline antipsychotic dose- n.i.
Interventions	1. Drug: flupenthixol i.m., chlorpromazine, haloperidol, pimozide, trifluoperazine Flexible dose. Allowed dose range: no upper limit, but lower limit was flupenthixol i.m. 40mg/month, chlorpromazine 200mg/day, haloperidol 3mg/day, pimozide 4mg/day, trifluoperazine 5mg/day.Mean dose: flupenthixol 84mg/month (n=31), chlorpromazine 366mg/day (n=3), haloperidol 11.8mg/day (n=3), pimozide 7.8mg/day (n=5), trifluoperazine 11.5mg/day (n=12). N=54 2. Placebo: Duration of taper (days): 30 days on drug, then received half dose for 30 days before they were put on placebo. N=66 Rescue medication: antiparkinson medication, antidepressants, anxiolyties
Outcomes	Examined: Relapse: rehospitalisation or rehospitalisation thought necessary although not possible or need of medication Unable to use / Not included:

	Hallucinations, delusions (no data / no predefined outcomes of interest)
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random, no further details.
Allocation concealment (selection bias)	Unclear risk	Allocation lists prepared by pharmacy for five antipsychotic drugs mentioned below, concealment is unclear
Blinding of participants and personnel (performance bias)	Low risk	Double, no further details.
Blinding of outcome assessment (detection bias)	Low risk	Double, no further details.
Incomplete outcome data (attrition bias)	Low risk	No clear bias. overall rate of leaving early of 11% is acceptable. Survival curve analysis was used for the primary outcome relapse
Selective reporting (reporting bias)	Low risk	No evidence for selective reporting.
Other bias	High risk	Blind was broken when a participant relapsed.

Doddi 1979

Methods	Randomisation: no details (just reported as a “randomised study”). Allocation: procedure not described. Blinding: ”double-blind” (“patients and authors were not aware of the allocated treatment”). Duration: 9 months. Design: randomised, parallel (enriched design: patients, who responded to fluphenazine long-acting treatment (25 or 50 mg/month) for at least six to 12 months before study entry, were randomised to continue that treatment or to placebo). Ten out of 20 patients had been previously recruited in a study comparing fluphenazine with trifluorazine. Location: no clear details. Setting: outpatients.
Participants	Diagnosis: chronic schizophrenia with an acute episode within 6 to 12 months before study entry (no details about diagnostic criteria) N=20. Gender: all men. Age: 19 to 32 years. History: duration stable at least sixmonths, duration ill- some were first episode patients, some were patients with recurrence, number of previous hospitalisations- no data, age at onset- no data, severity of illness- fluphenazine group had a mean BPRS baseline score of 24.56 (SD 3.56); placebo group had a mean BPRS baseline score of 21.71, baseline antipsychotic dose (25 or 50 mg/month)
Interventions	1.Drug: fluphenazine depot. Fixed dose: 25 or 50 mg/month (long-acting formulation). Mean dose: n.i..N=10 randomised (but data available only for 9 patients who completed the study) 2. Placebo: Duration of taper (days): n.i.. N=10 randomised (but data available only for 7 patients who completed the study) Rescue medication: antiparkinson medication at study entry (and then progressively tapered off, without a prespecified schedule)
Outcomes	Examined: Relapse: defined as worsening of clinical status needing an adjunctive new antipsychotic treatment Unable to use / Not included: Mental state: BPRS (no prespecified outcome of interest).
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details (just reported as a ”randomised study”).
Allocation concealment (selection bias)	Unclear risk	Procedure not described.
Blinding of participants and personnel (performance bias)	Low risk	Double-blind (“patients and authors were not aware of the allocated treatment”)
Blinding of outcome assessment (detection bias)	Low risk	Double-blind (”patients and authors were not aware of the allocated treatment”)
Incomplete outcome data (attrition bias)	Unclear risk	25% of the participants dropped out, all due to relapse. This may still be acceptable
Selective reporting (reporting bias)	Low risk	No evidence for selective reporting.
Other bias	Low risk	No clear other bias.

Eklund 1991

Methods	Randomisation: random, no further details. Allocation: procedure not described. Blinding: double, placebo injections, no further details. Duration: 48 weeks. Design: parallel. Location: single-centre. Setting: in- and outpatients.
Participants	Diagnosis: schizophrenia (Research Diagnostic Criteria), requiring neuroleptic maintenance treatment to prevent relapse N=43. Gender: n.i.. Age: mean 51.7 (range 25-65) years. History: duration stable- remained in the study after 15 weeks of haloperidol decanoate, duration ill- n.i., number of previous hospitalisations- n.i., age at onset- n.i., severity of illness- n.i., baseline antipsychotic dose- 60mg haloperidol decanoate per month (~3. 5mg/day haloperidol)
Interventions	1. Drug: haloperidol decanoate 60mg/4 weeks. Fixed dose. N=20 2. Placebo: Duration of taper: 0 days, but all on depot medication before study. N=23 Rescue medication: anticholinergics and sedation.
Outcomes	Examined: Relapse: clinical judgement. Leaving the study early. Unable to use / Not included: Mental state: Comprehensive Psychopathological Rating Scale (no mean, no SD / no prespecified outcome of interest) Adverse effects: extrapyramidal side-effects, tardive dyskinesia (no mean, no SD / continuous side-effect results were not among the prespecified outcomes) Physiological measures: laboratory (prolactin and haloperidol levels, no mean/SD / no prespecified outcomes of interest)
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random, no further details.
Allocation concealment (selection bias)	Unclear risk	Random, no further details.
Blinding of participants and personnel (performance bias)	Unclear risk	Double, placebo injections, no further details.
Blinding of outcome assessment (detection bias)	Unclear risk	Double, placebo injections, no further details.
Incomplete outcome data (attrition bias)	High risk	A considerable number of participants (42%) left the study early.The number was clearly higher in the placebo group and the reasons differed. Data were analysed on an intent-to-treat basis
Selective reporting (reporting bias)	Low risk	No selective reporting.
Other bias	Unclear risk	No clear other bias.

Hirsch 1973

Methods	Randomisation: randomly allocated by research assistant. Allocation: a part from the research assistant no one knew who was on drug or placebo until the data were analysed. Blinding: double, sesame oil injections, unmarked ampoules. Blinding was tested at the end of the trial and it worked. Duration: 9 months. Design: parallel. Location: two centres. Setting: outpatient.
Participants	Diagnosis: chronic schizophrenia (Present State Examination), chronicity defined by at least 2 admissions or 1 admission lasting longer than 6 months, 71 schizophrenic psychosis with delusions or auditory hallucinations, six non affective delusional psychoses, three catatonic schizophrenia N=81. Gender: 52 men, 29 women. Age: mean 43.4 years. History: duration stable- at least 8 weeks, duration ill- n.i., number of previous hospitalisations- 24 had ≤ 3 and 57 had ≥ 4), age at onset- n.i., severity of illness- n.i., baseline antipsychotic dose- 86% fluphenazine depot 25mg/month, no additional antipsychotic medication

Interventions	1. Drug - Fixed/flexible dose: Allowed dose range: 25mg/month - no upper limit. Mean dose: 26.4mg/month. N=41 2. Placebo: Duration of taper: n.i.. N=40. Rescue medication: antidepressants, antiparkinson medication
Outcomes	Examined: Relapse: deterioration of condition to a degree that participant had to be taken out of the trial to ensure that active medication was prescribed, prescription of oral phenothiazines Adverse effects: use of antiparkinson medication. Unable to use / Not included: Mental state: Present State Examination (no data / no predefined outcome of interest) Social functioning: Social Performance Schedule, Events Schedule of Bron and Birley (both no predefined outcome of interest)
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly allocated by research assistant.
Allocation concealment (selection bias)	Low risk	Apart from the research assistant no one knew who was on drug or placebo until the data were analysed
Blinding of participants and personnel (performance bias)	Low risk	Double, sesame oil injections, unmarked ampoules. Blinding was tested at the end of the trial and it worked
Blinding of outcome assessment (detection bias)	Low risk	Double, sesame oil injections, unmarked ampoules. Blinding was tested at the end of the trial and it worked
Incomplete outcome data (attrition bias)	Unclear risk	Overall, 43% of the participants left the study early (no complete ITTfor some outcomes)
Selective reporting (reporting bias)	Low risk	No evidence for selected reporting
Other bias	Low risk	No evidence of other bias

Hogarty 1973

Methods	Randomisation: randomly assigned, no further details. Allocation: procedure not described. Blinding: double, identical capsules, no further details. Duration: 2-3 years (data available up to 2 years). Design: parallel. Location: three centres. Setting: outpatient.
Participants	Diagnosis: schizophrenia (DSM-II, undifferentiated type 46.3%, paranoid 39%, acute differentiated 8%, schizoid affective 2.7%, other 3.8%), currently hospitalised for less than 2 years N=374. Gender: 159 men, 215 women. Age: mean 34.4 years. History: duration stable- 2 months transition phase, those who relapsed during this time were replaced, duration ill- n.i., number of previous hospitalisations- mean 2.6, age at onset- n.i., severity of illness- n.i., baseline antipsychotic dose- mean 265mg chlorpromazine per day
Interventions	Previous medication was gradually shifted to chlorpromazine for two months. 1. Drug: chlorpromazine - Flexible dose. Allowed dose range: 100mg/day. Mean dose: ~ 260mg/day. N=192 2. Placebo: Duration of taper: 0 days. N=182. Rescue medication: not indicated, but probably not allowed.
Outcomes	Examined: Relapse: clinical deterioration of suchmagnitude that hospitalisation appeared imminent Unable to use / Not included: Leaving the study early (numbers not specified for each group separately) Mental state: Brief Psychiatric Rating Scale, Inpatient Multidimensional Psychiatric Scale, Springfield Symptom Index, Hopkin's Symptom Distress Check List (all no SDs and data only given for subgroups / no predefined outcome of interest) Social behaviour and adjustment: Katz Adjustment Scale, Major Role Adjustment Inventory (both no SDs and data presented only for subgroups / no predefined outcome of interest)
Notes	Half of the participants randomly received major role therapy in addition to chlorpromazine or placebo. For the purpose of this review the four resulting groups were pooled as described above

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned, no further details.
Allocation concealment (selection bias)	Unclear risk	Procedure not described.
Blinding of participants and personnel (performance bias)	Low risk	Double, identical capsules, no further details.
Blinding of outcome assessment (detection bias)	Low risk	Double, identical capsules, no further details.
Incomplete outcome data (attrition bias)	Low risk	Relatively few participants left the study early due to reasons other than relapse which was the only outcome (n=31). Although it is unclear in which group they occurred the small percentage does not represent an important risk of bias
Selective reporting (reporting bias)	Low risk	No clear evidence for selective reporting.
Other bias	Low risk	No clear other bias. Maintenance

Hough 2010

Methods	Randomisation: patients were randomised in a 1 to 1 ratio (via a sponsor prepared, computer generated randomisation scheme, assigned by an interactive voice system). Allocation: interactive voice system. Blinding: double, no further details. Duration: variable (the trial was terminated early after an interim analysis). Design: parallel. Location: multi-centre. Setting: n.i..
Participants	Diagnosis: schizophrenia (DSM-IV-TR). N=410. Gender: 220 men, 88 women. Age: mean 39 years. History: duration stable- 12 weeks prospectively stable on fixed dose paliperidone, duration ill- mean 12 years, number of previous hospitalisations- median 2.6, age at onsetmean 27.3 years, severity of illness- PANSS total mean 53 points, baseline antipsychotic dose- n.i.
Interventions	1. Drug: paliperidone palmitate depot - Fixed dose: originally 25, 50 or 100mg/4 weeks; this dose was maintained. Mean dose: n.i.. N=206 2. Placebo: Duration of taper: 0 days. N=204. Rescue medication: n.i..
Outcomes	Examined: Relapse: psychiatric rehospitalisation, deliberate self-injury or violent behaviour, suicidal or homicidal ideation, certain predefined PANSS score Leaving the study early. Rehospitalisation. Death natural causes and suicide. Unable to use / Not included: Mental state: Positive and Negative Syndrome Scale (no predefined outcome of interest) Adverse effects: open interviews (only a few adverse events were indicated and these were not of interest for the review) Prolactin levels (no predefined outcome of interest).
Notes	The study was stopped early after a significant interim analysis

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised in a 1 to 1 ratio (via a sponsor prepared, computer generated randomisation scheme, assigned by an interactive voice system)
Allocation concealment (selection bias)	Low risk	Interactive voice system.
Blinding of participants and personnel (performance bias)	Low risk	Double, no further details.
Blinding of outcome assessment (detection bias)	Low risk	Double, no further details.
Incomplete outcome data (attrition bias)	High risk	Overall high drop-out rate (45%). Clearly more participants in the placebo group (95) than in the drug group (31) left the study early due to relapse. This imbalance may have biased the results of other outcomes such as adverse events. Kaplan-Meier survival curve analysis was used for the primary outcome relapse

Selective reporting (reporting bias)	Low risk	Those adverse events that occurred in at least 2% of the participants and severe adverse events were presented. We feel that's acceptable
Other bias	High risk	Study was stopped early after an interim analysis.

Kane 2011

Methods	Randomized controlled trial, parallel group Multinational Outpatients only patients already stabilised on asenapine were eligible for the trial 26 weeks
Participants	Stable schizophrenia Did not enter randomised double-blind treatment if: PANSS total > 75; CGI-S > 3; PANSS item scores >=4 on 'unusual thought content', 'conceptual disorganization', hallucinatory behavior', 'hostility', 'uncooperativeness' Mean age: 39 y 54-60% male Age at first diagnosis: 26 y
Interventions	1. Asenapine sublingual, mean dose: 17.6 (4.2) mg/d 2. Placebo 26 weeks
Outcomes	Relapse at longest follow-up. Relapse defined as: CGI-S >=4 AND PANSS-total score increase >=20%, a PANSS item score>=5 on 'hostility' or 'uncooperativeness', or a PANSS item score >=5 on 2 items of 'unusual thought content', 'conceptual disorganisation', 'hallucinatory behaviour' OR risk of violence to self/others, increase in suicide risk, additional medication (above allowed in the trial) required Time to relapse Weight gain Adverse effects
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomized, not further described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	Double-blind, asenapine and placebo were identical in appearance, taste and flavor
Blinding of outcome assessment (detection bias)	Low risk	Neither patients nor sites were aware of the tablet identify
Incomplete outcome data (attrition bias)	High risk	High dropout in the placebo arm
Selective reporting (reporting bias)	Low risk	No evidence of selective outcome reporting
Other bias	Unclear risk	Role of funding body not explained

Kane 2012

Methods	Randomized controlled trial, parallel group Only patients already stabilised on AP treatment were included in the maintenance phase Supported by Otsuka Pharmaceuticals 52 weeks but stopped before time due to interim analysis 8.6% in ARI group completed 52 weeks of treatment, 2.2% in PCB group Multinational study Outpatients
Participants	Inclusion criteria for maintenance phase: Outpatient, Panns<80, lack of specific psychotic symptoms, CGI-s <4, CGI-ss<2 Exclusion criteria: clinically significant medical disorder, abnormal laboratory test or ECG, treatment refractory, responsive to clozapine Mean age: 40-41 y 60% male Age at first diagnosis: 26 y
Interventions	1. Aripiprazole IM-depot, 400 mg/month 2. Placebo IM-depot
Outcomes	Relapse at longest follow-up: relapse defined as meeting any/all of following criteria: clinical worsening (CGI>=5, increase on certain PANSS items, hospitalisation due to worsening of psychotic symptoms, risk of suicide, violent behaviour (self-injury, injury to another person, or property damage) Time to relapse Leaving the study early Suicide + attempt Adverse effects Weight gain

Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomized, not further specified
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	Double-blind, not further described
Blinding of outcome assessment (detection bias)	Low risk	Probably done
Incomplete outcome data (attrition bias)	Unclear risk	<10% of participants completed 52 weeks of study duration, because early termination of trial acceptable drop out in intervention arm, higher in placebo arm
Selective reporting (reporting bias)	Low risk	No evidence of selective outcome reporting
Other bias	Unclear risk	Unclear role of funding source (Otsuka Pharmaceuticals)

Kramer 2007

Methods	Randomisation: randomised, computerized randomisation and stratification scheme. Allocation: interactive voice-response system. Blinding: double, no further details. Duration: variable. Design: parallel. Location: multi-centre. Setting: outpatient, sponsored.
Participants	Diagnosis: schizophrenia (DSM-IV), 80%paranoid subtype, 14%undifferentiated subtype, initially with acute exacerbation, then 8 weeks run in and 6 weeks stabilisation phase N=207. Gender: 121 men, 86 women. Age: 38.3 years. History: duration stable- at least 8 weeks, duration ill- mean 12.1 years, number of previous hospitalisations- median 3, age at onset- 26.2 years, severity of illness- mean PANSS total score 52.2, mean CGI severity 2.6, baseline antipsychotic dose- 10.8mg/ day paliperidone
Interventions	1. Drug: paliperidone- Flexible doses. Allowed dose range: 3 - 15mg/day Mean dose: 10. 8 mg/day. N=105 2. Placebo: Duration of taper: 0 days. N=102. Rescuemedication: benzodiazepines, antiparkinson medication, propanolol, antidepressants when the dose was stable for at least 3 months before the study
Outcomes	Examined: Relapse: (a) psychiatric hospitalisation (involuntary or voluntary admission); b) increase in Positive and Negative Syndrome Scale (PANSS) total score by 25% for 2 consecutive days for patients who scored more than 40 at randomisation or a 10-point increase for patients who scored 40 or below at randomisation; c) increase in the Clinical Global Impression-Severity (CGI-S) score to at least 4, for patients who scored 3 or below at randomisation, or to at least 5, for patients whose CGI-S scores were 4 at randomisation, for 2 consecutive days; d) deliberate self-injury or aggressive behavior, or suicidal or homicidal ideation and aggressive behavior that was clinically significant; e) increase in prespecified individual PANSS item scores to at least 5, for patients whose scores were 3 or below at randomisation, or to at least 6, for patients whose scores were 4 at randomisation, for 2 consecutive days) Quality of life: Schizophrenia Quality-of-Life Scale. Unable to use / Not included: Mental state: PANSS (no predefined outcome of interest). Behaviour: suicide, aggression (only mean scores which were no predefined outcomes of interest) Functioning: Personal and Social Performance Scale (no predefined outcome of interest) Global state:CGI-severity (onlymean scorewhichwas no predefined outcome of interest) Adverse effects: World Health Organization Adverse Reaction Terminology dictionary (no data / no predefined outcome of interest), movement disorders (Simpson Angus Scale, Barnes Akathisia Rating Scale, and Abnormal InvoluntaryMovement Scale (all no data / continuous side-effect results were not among the predefined outcomes of interest) Physiological measures: laboratory (except for metabolic problems no data), vital signs, ECG, prolactin (all no data / no predefined outcomes of interest)
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, computerized randomisation and stratification scheme
Allocation concealment (selection bias)	Low risk	Interactive voice-response system.
Blinding of participants and personnel (performance bias)	High risk	Double, no further details.
Blinding of outcome assessment (detection bias)	Low risk	Double, no further details.
Incomplete outcome data (attrition bias)	High risk	Only 28 out of 207 participants left the study prematurely for another reason than relapse. Therefore, missing outcomes may not pose a problem for the primary outcome which was assessed with the Kaplan-Meier method. Nevertheless, high discontinuations due to relapse (75/207) which were much more frequent in the placebo group than in the drug group pose a major problem for secondary outcomes. No full ITT (participants had to receive at least one dose post-baseline) but only two participants were excluded on this basis
Selective reporting (reporting bias)	Low risk	No evidence for selective reporting.
Other bias	High risk	Study was terminated after an interimanalysis showed a clear advantage of paliperidone

Leff 1971

Methods	Randomisation: random, no further details. Allocation: trial medication was held by the unit secretary and dispensed to Julian Leff who gave it to the treating consultant. Only the unit secretary knew which pills were active drug and which were placebo. Blinding: double, no further details. But side-effects were not troublesome in any patient and therefore doctors concerned probably received no clues about whether a patient was on active drug or not. Duration: one year. Design: parallel. Location: single-centre. Setting: outpatient.
Participants	Diagnosis: schizophrenia (Present State Examination), recently recovered from an acute episode, 32 florid schizophrenia, 3 delusional psychosis N=35. Gender: n.i.. Age: 16-55 years. History: duration stable- n.i., but stabilised at the pre-admission level during a 6-12 weeks outpatient period and recently recovered from an acute episode, duration ill- n. i., number of previous hospitalisations- n.i., age at onset- n.i., severity of illness- n.i., baseline antipsychotic dose- n.i.
Interventions	1. Drug: trifluoperazine or chlorpromazine (depending on the previous medication so that so far as the patient was concerned there was no apparent change in medication) . Flexible dose. Allowed dose range: trifluoperazine 5-25mg/day, chlorpromazine 100-500mg/day.Mean dose: chlorpromazine 157.1 mg/day, trifluoperazine 12.3mg/day. N= 20 2. Placebo: Duration of taper: not indicated, probably 0 days. N=15 Rescue medication: antiparkinson medication, antidepressants, no antipsychotics (doctors received a letter asking them not to prescribe other medication)
Outcomes	Examined: Relapse: physician was sufficiently concerned about the patient's status to want to be certain that he was on active drug Leaving the study early.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random, no further details.
Allocation concealment (selection bias)	Low risk	Trialmedication was held by the unit secretary and dispensed to Julian Leff who gave it to the treating consultant. Only the unit secretary knew which pills were active drug and which were placebo

Blinding of participants and personnel (performance bias)	Low risk	Double, no further details. But side-effects were not troublesome in any patient and therefore doctors concerned probably received no clues about whether a patient was on active drug or not
Blinding of outcome assessment (detection bias)	Low risk	Double, no further details. But side-effects were not troublesome in any patient and therefore doctors concerned probably received no clues about whether a patient was on active drug or not
Incomplete outcome data (attrition bias)	High risk	Overall drop-out rate was 60%, almost all due to relapse which occured much more frequently in the placebo group. This poses a problem for other outcomes than relapse
Selective reporting (reporting bias)	Low risk	No evidence for selective reporting.
Other bias	Low risk	No clear other bias.

McCreadie 1989

Methods	Randomisation: assumed, because study was double-blind and because the first study phase was randomised (no further details). Allocation: procedure not described. Blinding: double, no further details. Duration: 12 months. Design: parallel. Location: single-center. Setting: outpatient.
Participants	Diagnosis: first episode schizophrenia (Present State Examination, Feighner criteria and Research Diagnostic Criteria) N=15. Gender: n.i. Age: n.i. History: duration stable- 1 year, duration ill- n.i., number of previous hospitalisationsn. i., age at onset- n.i., severity of illness- n.i., baseline antipsychotic dose- n.i.
Interventions	1. Drug: pimozide once weekly or i.m. flupenthixol. Flexible doses. Allowed dose range: n.i.. Mean dose: n.i.. N=8. 2. Placebo: Duration of taper: 0 days N=7. Rescue medication: antiparkinson medication.
Outcomes	Examined: Relapse: re-admission. Unable to use / Not included: Leaving early (no data). Cognition (no data for withdrawal study / no predefined outcome of interest) Adverse effects: parkinsonism, tardive dyskinesia (no data for withdrawal study)
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation assumed.
Allocation concealment (selection bias)	Unclear risk	Procedure not described.
Blinding of participants and personnel (performance bias)	Low risk	Double, no further details.
Blinding of outcome assessment (detection bias)	Low risk	Double, no further details.
Incomplete outcome data (attrition bias)	Unclear risk	It is unclear whether there were missing data.
Selective reporting (reporting bias)	Low risk	No evidence for selective reporting.
Other bias	Unclear risk	Not entirely clear.

Merjerrison 1964

Methods	Randomisation: randomly assigned. Allocation: procedure not described. Blinding: double - (apart from previous antipsychotic group) - three different colours which were again changed.Double-blind condition maintained for patients, ward nurses and psychiatrists. Duration: 7 months. Design: parallel. Location: single-centre. Setting: inpatient.

Participants	Diagnosis: chronic psychotic patients, treatment resistive in closed wards. No seizures, no antidepressants, no candidates for discharge N=88. Gender: 38 men, 40 women. Age: 47 years. History: duration stable- 1 year onmedication, duration ill- n.i., number of previous hospitalisations- n.i., age at onset- mean 28.1 years, severity of illness- mean 11.6 on modified Psychotic Reaction Profile (PRP), baseline antipsychotic dose- 39.3mg/ 3 weekly fluphenazine decanoate
Interventions	1. Drug: trifluoperazine (10-90 mg/day), chlorprothixene (50-450 mg/day), same medication (various drugs). Flexible doses. Allowed dose range: n.i..Mean dose: n.i.. N=54. 2. Placebo: Duration of taper: 0 days. N=34. Rescue medication: antiparkinson, barbiturate sedation.
Outcomes	Examined: Relapse: clinical judgement. Unable to use / Not included: Ward behaviour: unpublished rating scale (no predefined outcome of interest) Urinary excretion (no predefined outcome of interest).
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random, no further detail
Allocation concealment (selection bias)	Unclear risk	Procedure not described.
Blinding of participants and personnel (performance bias)	Unclear risk	Double, different colours.
Blinding of outcome assessment (detection bias)	Low risk	Double, different colours.
Incomplete outcome data (attrition bias)	Low risk	Drop-outs 10 out of 88 is acceptable (11%) , although only completers were analysed
Selective reporting (reporting bias)	Low risk	No evidence for selective reporting.
Other bias	Low risk	No evidence for other bias.

Pfizer 2000

Methods	Randomisation: randomised, computer-generated randomised code. Allocation: Treatment cards numbered for each subject entering double-blind phase, investigator and pharmacist was to allocate numbers to subjects in strict sequence of entry to study. Blinding: double, identical capsules in blisters. Duration: 52 weeks. Design: parallel. Location: multi-centre. Setting: inpatient.
Participants	Diagnosis: chronic or subchronic schizophrenia DSM-III-R. N=146. Gender: 39 women, 107 men. Age: mean 50 years. History: duration stable- n.i., duration ill- mean 21.5 years, number of previous hospitalisations- mean 10.7, age at onset- mean 27.7 years, severity of illness- PANSS 87.1, baseline antipsychotic dose- n.i.
Interventions	1. Drug: ziprasidone. Fixed dose. Allowed dose range: 160 mg/day.Mean dose: 160mg/ day. N=71 2. Placebo: Duration of taper: 0 days. N=75. Rescuemedication: other antipsychotics not allowed, concomitant medication formovement disorders, hypnotics, sedatives, anxiolytics
Outcomes	Examined: Relapse: as defined by CGI-Improvement scale of 6 or more and/or score of 6 or more on PANSS items P7,G8 on two successive days Adverse effects: number of participants with at least one adverse event, akathisia, dyskinesia, dystonia, tremor, use of antiparkinson medication, weight gain Unable to use / Not included: Global state: mean Clinical Global Impression Severity Scale (no means, no SDs / no predefined outcome of interest) Mental state: Brief Psychiatric Rating Scale, AMDP system, Paranoid Depression Scale (all no means, no SDs / no predefined outcomes of interest) Functioning: Global Assessment Scale (no mean, no SD / no predefined outcome of interest) Subjective well-being (own scale - no mean, no SD). Adverse effects: extrapyramidal side-effects (Aquired Involuntary Movement Scale - no SD, Simpson Angus Scale, Dosage Record and Treatment Emergent Symptoms Scale - all no means, no SDs / continuous side-effect results were not among the prespecified outcome)

	Concept of illness (concept of illness scale - no mean, no SD / no predefined outcome of interest) Physiological measures: routine laboratory, ECG, EEG physical exams and vital signs (all no data / no predefined outcome of interest) Pharmacokinetics (no predefined outcome of interest). Compliance: doctors' assessment (no predefined outcome of interest)
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomised code.
Allocation concealment (selection bias)	Low risk	Treatment cards numbered for each subject entering double-blind phase, investigator and pharmacist was to allocate numbers to subjects in strict sequence of entry to study
Blinding of participants and personnel (performance bias)	Low risk	Double, identical capsules.
Blinding of outcome assessment (detection bias)	Low risk	Double, identical capsules.
Incomplete outcome data (attrition bias)	High risk	68% overall dropout, most due to relapse, which occured much more frequently in the placebo group, thus not a problem for this outcome and for drop-out but for other outcomes
Selective reporting (reporting bias)	Low risk	No evidence for selective reporting.
Other bias	Low risk	No evidence for other bias.

Pietzcker 1993

Methods	Randomisation: centrally randomised by a specialised unit using an "adaptive randomisation method". Allocation: procedure not described. Blinding: open, only key rating scales were additionally rated by a second blind assessor. Duration: 2 years. Design: parallel. Location: multi-centre. Setting: outpatient.
Participants	Diagnosis: schizophrenia or schizoaffective disorder (ICD-9 and Research Diagnostic Criteria) N=237. Gender: 124 women, 113 men. Age: mean 34.6 years. History: duration stable- at least 3 months in addition titrated to minimally effective dose which was maintained for at least 4 weeks, duration ill- mean 7.3 years, number of previous hospitalisations- n.i., age at onset- mean 27.3 years, severity of illness- mean CGI 3.8; mean BPRS total score 28.5, baseline antipsychotic dose- n.i.
Interventions	1. Drug: various antipsychotic drugs. Flexible dose, minimum 100mg/day chlorpromazine equivalent. Allowed dose range: 100 - unlimited chlorpromazine equivalents/ day. Mean dose: 201 mg/day. N=122 2.No treatment (=crisis management, medication was only given in case of a full relapse) . Duration of taper: 50% every two weeks, thus after 6 weeks only 12.5% of initial dose left, thus 42 days. Note that participants were not withdrawn after they had received crisis intervention. N=115 Rescuemedication: in the no treatment group additional antipsychoticmedication could only be given in case of relapse
Outcomes	Examined: Relapse: Brief Psychiatric Rating Scale total score - >10 increase, Global Assessement Scale <20 reduction, deterioration Clinical Global Impression Scale CGI >7 Unable to use / Not included: Global state: Clinical Global Impression (no means, no SDs / no predefined outcome of interest) Mental state: Brief Psychiatric Rating Scale, AMDP system, Paranoid Depression Scale (all no means, no SDs / no predefined outcome of interest) Functioning: Global Assessment Scale (no mean, no SD / no predefined outcome of interest) Subjective well-being (own scale - no mean, no SD / no predefined outcome of interest) Adverse effects: extrapyramidal side-effects (Aquired Involuntary Movement Scale - no SD, Simpson Angus Scale, Dosage Record and Treatment Emergent Symptoms Scale - all no means, no SDs / continuous side-effect results were not among the predefined outcomes of interest) Concept of illness (concept of illness scale - no mean, no SD) Compliance: doctors' assessment (no predefined outcome of interest) Physiologicalmeasures: routine laboratory, ECG, EEG(no data / no predefined outcome

	of interest)
Notes	There was a third group using intermittent treatment which was not of interest for this review

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centrally randomised by a specialised unit using an ”adaptive randomisation method”
Allocation concealment (selection bias)	Unclear risk	Procedure not described.
Blinding of participants and personnel (performance bias)	Unclear risk	Open, only key rating scales were additionally rated by a second blind assessor
Blinding of outcome assessment (detection bias)	Unclear risk	Open, only key rating scales were additionally rated by a second blind assessor
Incomplete outcome data (attrition bias)	High risk	High two year discontinuation rate of 43. 7%. Analysis was intention-to-treat based on Kaplan-Meier survival curve analysis, completer analyses were presented in addition if different. A risk of bias can not be excluded given the high discontinuation rate
Selective reporting (reporting bias)	Low risk	No evidence for selective reporting.
Other bias	Low risk	No evidence for selective reporting.

Sampath 1992

Methods	Randomisation: random, no further details. Allocation: procedure not described. Blinding: double, placebo was sesame oil of identical volume and identical in physical appearance. Duration: 12 months. Design: parallel. Location: single-centre. Setting: inpatient, sponsored.
Participants	Diagnosis: chronic schizophrenia (Research Diagnostic Criteria), stable for at least 5 years (absence of clinical deterioration and/or an increase of neuroleptic medication, retrospectively and in addition prospectively for at least 12 months), all on fluphenazine decanoate N=24. Gender: n.i.. Age: mean 57.3 years. History: duration stable- retrospectively at least 5 years, prospectively for 12 months, mean 7 years, duration ill- mean 33.1 years, number of previous hospitalisations- n.i. , but mean duration of hospitalisation 24.9 years (unclear whether current or life-time total), age at onset- mean 24.3 years, severity of illness- mean BPRS total score 24.9, baseline antipsychotic dose- mean 41.9 mg fluphenazine / 4 weeks
Interventions	1. Drug: fluphenazine decanoate.Fixed dose: mean 50.4mg/4 weeks. N=12 2. Placebo: Duration of taper: 0 days, but all participants were on depot medication before the study. N=12 Rescue medication: n.i., but probably not allowed.
Outcomes	Examined: Relapse: at least 25%increase of Brief Psychiatric Rating Scale total score and judgement of by nurse according to Psychotic Inpatient Profile Unable to use / Not included: Mental state: Brief Psychiatric Rating Scale total, Psychotic Inpatient Profile (for both scales means for subgroups only / no predefined outcome of interest) Physiological measures: prolactin levels (no SD’s / no predefined outcome of interest)
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random, no further details.
Allocation concealment (selection bias)	Unclear risk	Procedure not described.
Blinding of participants and personnel (performance bias)	Low risk	Double, placebo was sesame oil of identical volume and identical in physical appearance
Blinding of outcome assessment (detection bias)	Low risk	Double, placebo was sesame oil of identical volume and identical in physical appearance
Incomplete outcome data (attrition bias)	Unclear risk	There is no statement on participants leaving the study early

Selective reporting (reporting bias)	Low risk	No evidence for selective reporting.
Other bias	High risk	There was a baseline imbalance in terms of gender and in terms of baseline fluphenazine dose

Troshinsky 1962

Methods	Randomisation: randomised, no further details. Allocation: psychiatrist without contact to the participants held the key and filled the medication containers. Blinding: double, exact placebo replicas. Duration: ~ 43 weeks. Design: parallel. Location: single-centre. Setting: outpatient.
Participants	Diagnosis: schizophrenia without positive symptoms (clinical diagnosis) N=43. Gender: 16 men, 27 women. Age: typically 40-50 years. History: duration stable- out of hospital for at least a year (typically 2-4 years), duration ill- n.i., number of previous hospitalisations- typically 2-3, age at onset n.i., severity of illness n.i., but no positive symptoms at baseline, baseline antipsychotic dose- maximum 300mg chlorpromazine per day
Interventions	1. Drug: various phenothiazines, mainly chlorpromazine. Fixed/flexible dose: flexible. Allowed dose range: not limited, but complete discontinuation was not allowed. Mean dose: 150-200mg/day chlorpromazine. N=24 2. Placebo: Duration of taper: 0 days. N=19. Rescue medication: not allowed.
Outcomes	Examined: Relapse: clinical judgement. Service use: number of participants rehospitalised.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, no further details.
Allocation concealment (selection bias)	Low risk	Psychiatrist without contact to the participants held the key and filled the medication containers
Blinding of participants and personnel (performance bias)	Low risk	Double, exact placebo replicas.
Blinding of outcome assessment (detection bias)	Low risk	Double, exact placebo replicas.
Incomplete outcome data (attrition bias)	Unclear risk	Unclear - whether participants discontinued the study prematurelywas not reported
Selective reporting (reporting bias)	Low risk	No evidence for selective reporting.
Other bias	High risk	Some placebo participants continued to take medication, study terminated early

Footnotes

Characteristics of excluded studies

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

References to studies

Included studies

Andrews 1976

[Empty]

Arato 2002

[Empty]

Crow 1986

[Empty]

Doddi 1979

[Empty]

Eklund 1991

[Empty]

Hirsch 1973

[Empty]

Hogarty 1973

[Empty]

Hough 2010

[Empty]

Kane 2011

[Empty]

Kane 2012

[Empty]

Kramer 2007

[Empty]

Leff 1971

[Empty]

McCreadie 1989

[Empty]

Merjerrison 1964

[Empty]

Pfizer 2000

[Empty]

Pietzcker 1993

[Empty]

Sampath 1992

[Empty]

Troshinsky 1962

[Empty]

Excluded studies

Data and analyses

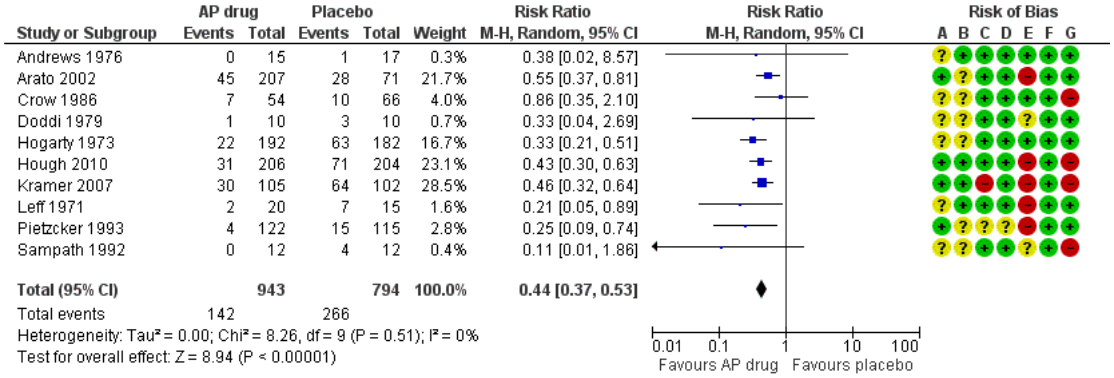
1 Maintenance AP drug treatment versus discontinuation (placebo)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Relapse up to 3 months	10	1737	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.37, 0.53]
1.2 Relapse from 7 months to 1 year	18	3038	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.32, 0.46]
1.3 Number of participants hospitalized (> 7 months)	8	1402	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.40, 0.66]
1.4 Adverse effects: weight gain >= 7% (7 to 12 months)	4	1145	Risk Ratio (M-H, Random, 95% CI)	2.83 [1.29, 6.20]
1.5 Adverse effects: at least one adverse event (7 to 12 months)	6	1826	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.88, 1.06]

1.6 Leaving the study early due to adverse events (> 7 months)	11	1782	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.46, 1.26]
1.7 Suicide (7 to 12 months)	4	1055	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.86]
1.8 Suicide attempt	2	610	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.07, 6.65]
1.9 Quality of life (7 to 12 months)	1	205	Std. Mean Difference (IV, Random, 95% CI)	-0.01 [-0.29, 0.26]
1.10 Functioning	2	346	Std. Mean Difference (IV, Random, 95% CI)	0.12 [-0.46, 0.70]
1.10.1 Global Assessment of Functioning (GAF)	1	141	Std. Mean Difference (IV, Random, 95% CI)	0.43 [0.09, 0.76]
1.10.3 Personal and Social Performance Scale (PSP)	1	205	Std. Mean Difference (IV, Random, 95% CI)	-0.17 [-0.44, 0.11]
1.11 Violent/aggressive behavior (7 to 12 months)	2	288	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.15, 0.60]

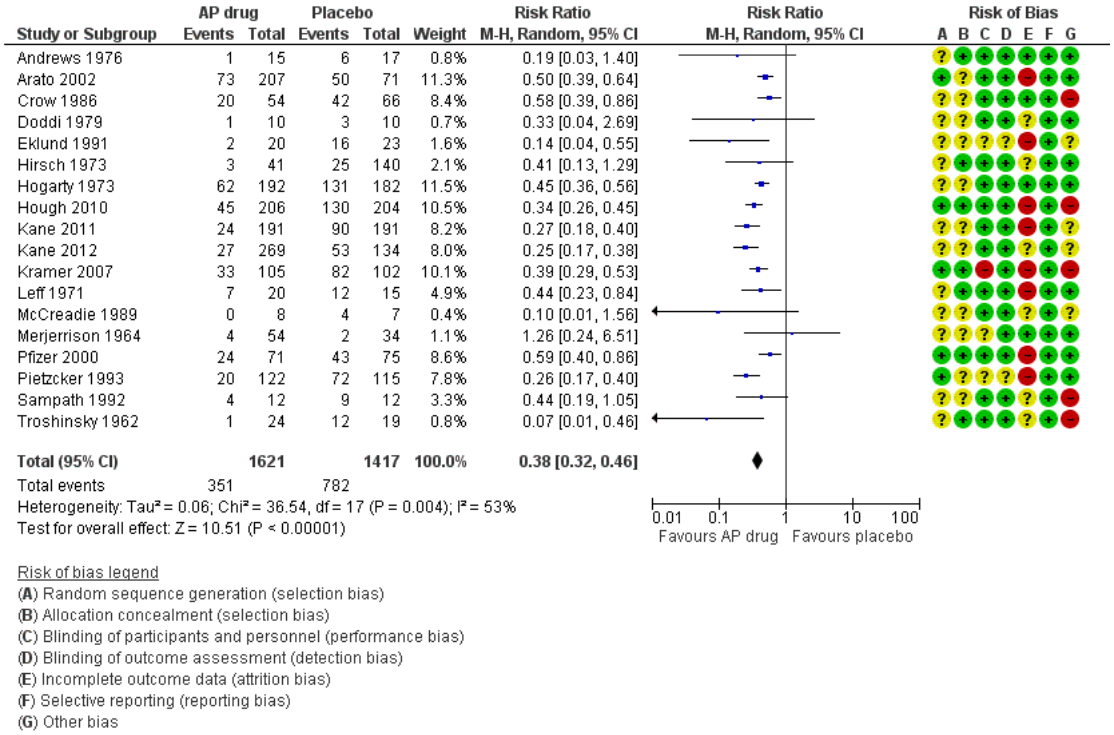
Figures

Figure 1 (Analysis 1.1)



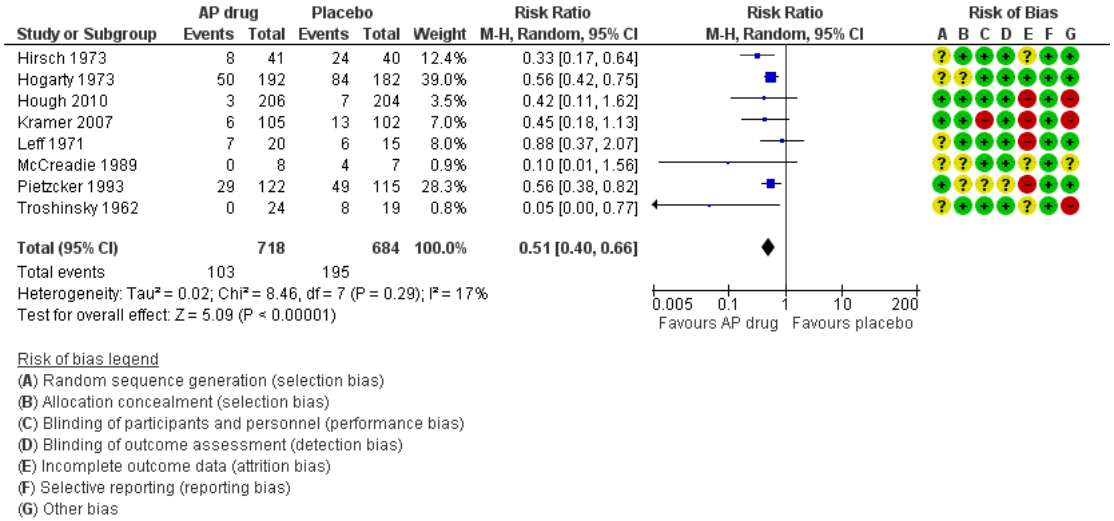
Forest plot of comparison: 1 Maintenance AP drug treatment versus discontinuation (placebo), outcome: 1.1 Relapse up to 3 months.

Figure 2 (Analysis 1.2)



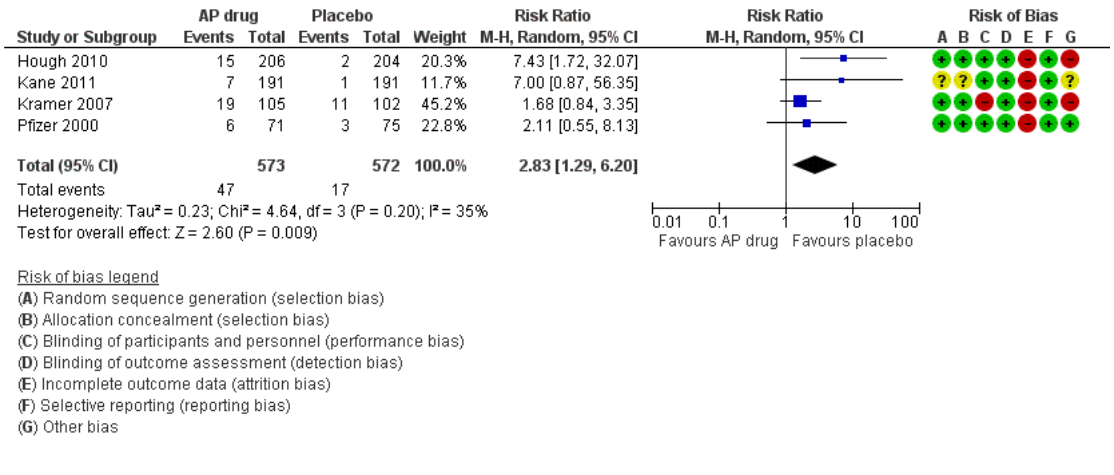
Forest plot of comparison: 1 Maintenance AP drug treatment versus discontinuation (placebo), outcome: 1.2 Relapse from 7 months to 1 year.

Figure 3 (Analysis 1.3)



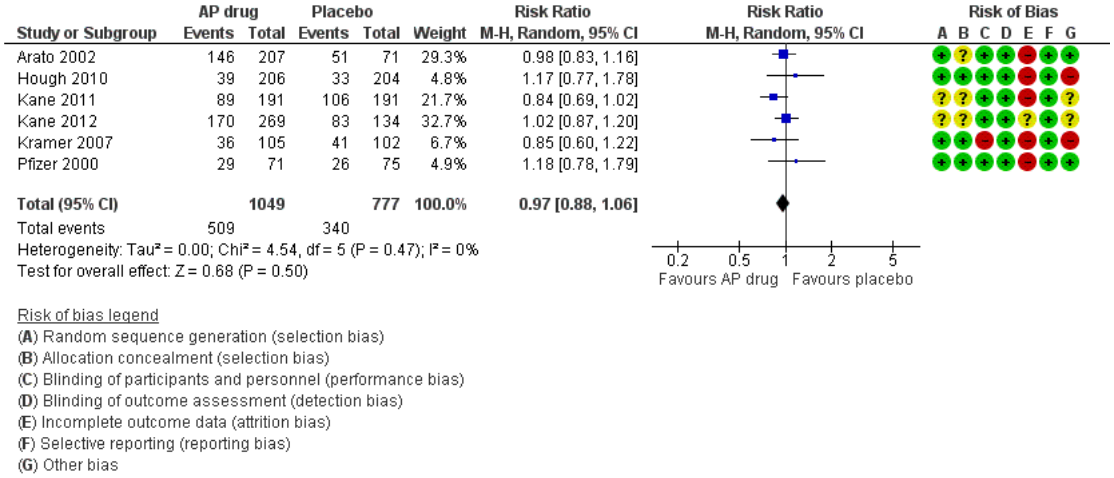
Forest plot of comparison: 1 Maintenance AP drug treatment versus discontinuation (placebo), outcome: 1.3 Number of participants hospitalized (> 7 months).

Figure 4 (Analysis 1.4)



Forest plot of comparison: 1 Maintenance AP drug treatment versus discontinuation (placebo), outcome: 1.4 Adverse effects: weight gain >= 7% (7 to 12 months).

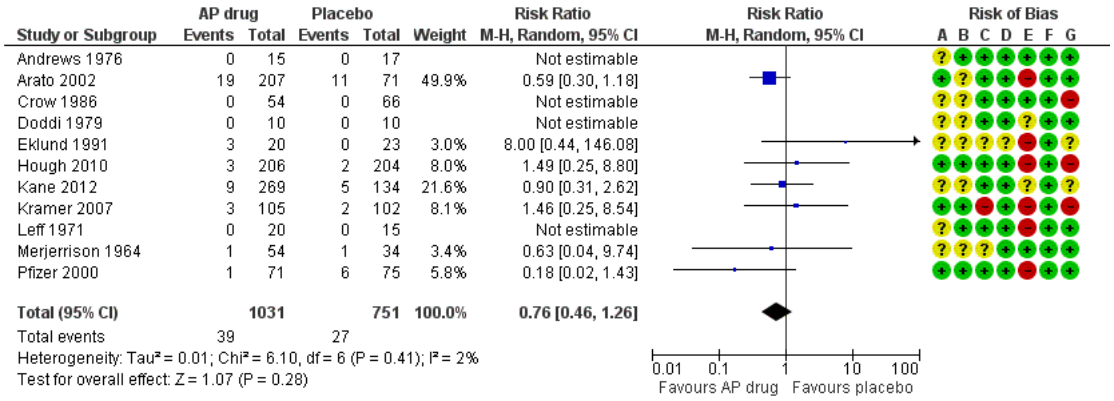
Figure 5 (Analysis 1.5)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 1 Maintenance AP drug treatment versus discontinuation (placebo), outcome: 1.5 Adverse effects: at least one adverse event (7 to 12 months).

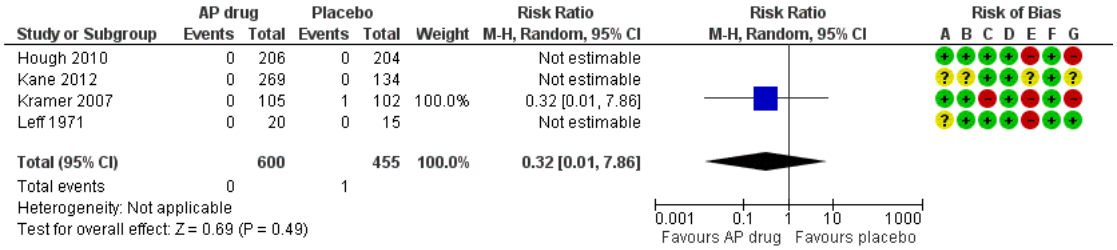
Figure 6 (Analysis 1.6)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 1 Maintenance AP drug treatment versus discontinuation (placebo), outcome: 1.6 Leaving the study early due to adverse events (> 7 months).

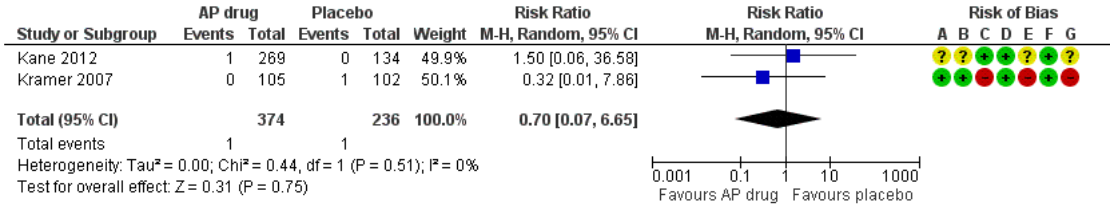
Figure 7 (Analysis 1.7)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 1 Maintenance AP drug treatment versus discontinuation (placebo), outcome: 1.7 Suicide (7 to 12 months).

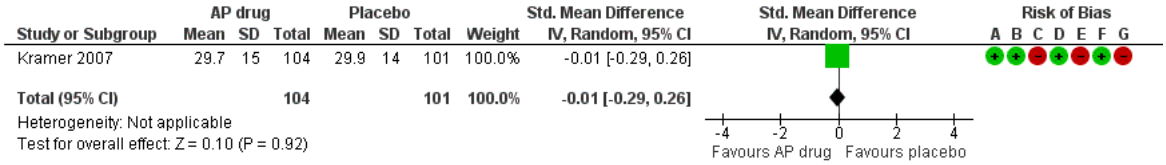
Figure 8 (Analysis 1.8)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 1 Maintenance AP drug treatment versus discontinuation (placebo), outcome: 1.8 Suicide attempt.

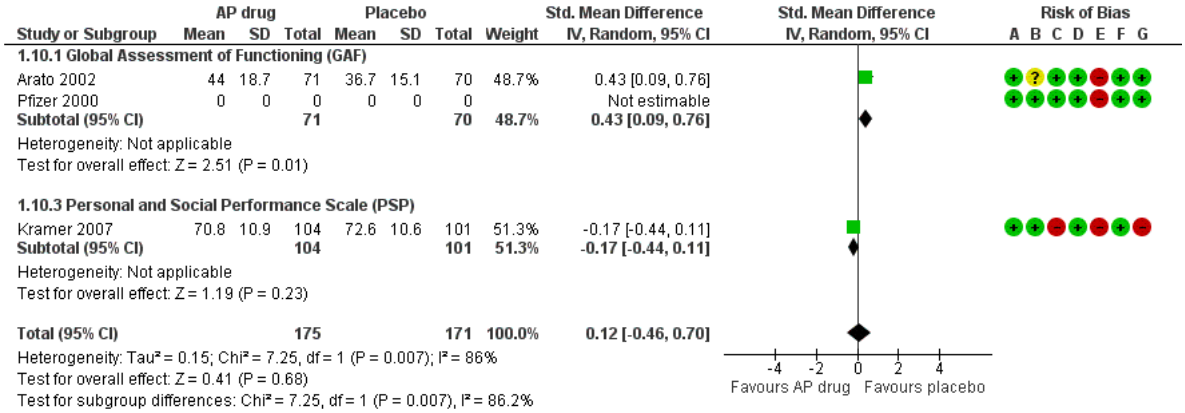
Figure 9 (Analysis 1.9)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 1 Maintenance AP drug treatment versus discontinuation (placebo), outcome: 1.9 Quality of life (7 to 12 months).

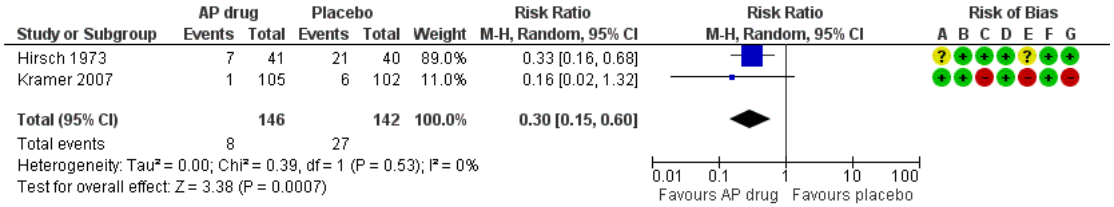
Figure 10 (Analysis 1.10)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 1 Maintenance AP drug treatment versus discontinuation (placebo), outcome: 1.10 Functioning.

Figure 11 (Analysis 1.11)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 1 Maintenance AP drug treatment versus discontinuation (placebo), outcome: 1.11 Violent/aggressive behavior (7 to 12 months).