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Antipsychotic combinations for schizophrenia (Review)

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[Intervention Review]

Antipsychotic combinations for schizophrenia

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ABSTRACT

Background

Many people with schizophrenia do not achieve a satisfactory treatment response with their initial antipsychotic drug treatment. Sometimes a second antipsychotic, in combination with the first, is used in these situations.

Objectives

To examine whether:

1. treatment with antipsychotic combinations is effective for schizophrenia; and
2. treatment with antipsychotic combinations is safe for the same illness.

Search methods

We searched the Cochrane Schizophrenia Group's register which is based on regular searches of CINAHL, BIOSIS, AMED, Embase, PubMed, MEDLINE, PsycINFO, and registries of clinical trials. There are no language, time, document type, or publication status limitations for inclusion of records in the register. We ran searches in September 2010, August 2012 and January 2016. We checked for additional trials in the reference lists of included trials.

Selection criteria

We included all randomised and quasi-randomised controlled trials comparing antipsychotic combinations with antipsychotic monotherapy for the treatment of schizophrenia and/or schizophrenia-like psychoses.

Data collection and analysis

We independently extracted data from the included studies. We analysed dichotomous data using risk ratios (RR) and the 95% confidence intervals (CI). We analysed continuous data using mean difference (MD) with a 95% CIs. For the meta-analysis we used a random-effects model. We used GRADE to complete a 'Summary of findings' table and assessed risk of bias for included studies.

Main results

Sixty-two studies are included in the review, 31 of these compared clozapine monotherapy with clozapine combination. We considered the risk of bias in the included studies to be moderate to high. The majority of trials had unclear allocation concealment, method of randomisation and blinding, and were not free of selective reporting.

There is some limited evidence that combination therapy may be superior to monotherapy in reducing the risk of no clinical response (RR 0.73 CI 0.64 to 0.83; participants = 2398; studies = 29; *very low-quality evidence*), subgroup analyses show that the positive result was due to the studies with clozapine in both the monotherapy and combination groups (RR 0.66 CI 0.53 to 0.83; participants = 1127; studies = 17) and typical in both groups (RR 0.64 CI 0.49 to 0.84; participants = 597; studies = 5). The subgroup with atypical antipsychotics in both groups did not showed a difference between the two interventions (RR 0.95 CI 0.83 to 1.09; participants = 674; studies = 7). Three studies provided data regarding relapse, the pooled data showed high heterogeneity (I^2 = 82%) and therefore the results were not pooled. Two studies showed no difference between the interventions and one study showed that antipsychotics combination might decrease the risk of relapse. A combination of antipsychotics was not superior or inferior to antipsychotic monotherapy in reducing the number of participants discontinuing treatment early (RR 0.90 CI 0.76 to 1.07; participants = 3137; studies = 43, *low-quality evidence*). No difference was found between treatment groups in the number of participants hospitalised (RR 0.96 CI 0.36 to 2.55; participants = 202; studies = 3, *very low-quality evidence*). We did not find evidence of a difference between treatment groups in serious adverse events or those requiring discontinuation (RR 1.05 CI 0.65 to 1.69; participants = 2398; studies = 30, *very low-quality evidence*). There is a lack of evidence on clinically important change in quality of life, with only four studies reporting average endpoint or change data for this outcome on three different scales, none of which showed a difference between treatment groups.

Authors' conclusions

Currently, most evidence regarding the use of antipsychotic combinations comes from short-term trials, limiting the assessment of long-term efficacy and safety. We found very low-quality evidence that a combination of antipsychotics may improve the clinical response. We also found very low-quality evidence that a combination of antipsychotics may make no difference at preventing participants from leaving the study early, preventing relapse and/or causing more serious adverse events than monotherapy.

PLAIN LANGUAGE SUMMARY

Combining antipsychotic medication for the treatment of schizophrenia

Background

Antipsychotic medication was introduced in the 1950s to reduce or alleviate the symptoms of schizophrenia, such as the psychotic states of hearing voices, visual hallucinations and strange thoughts such as paranoia (feeling singled-out or put upon by others). Medication for mental illness also helped to establish care in the community, because people could take medication in their homes or by regularly visiting the hospital. But this also led to new issues such as the effectiveness of different medication (taken alone or in combination) and compliance (the willingness of service users to take their medication without being supervised).

The range of antipsychotic medication available is wide and their effectiveness can also vary from individual to individual. In addition, not all patients fully respond to a single antipsychotic, and in these situations, a combination of antipsychotics are often prescribed. The evidence for the benefits of taking one or more antipsychotics in combination is often unclear. There are also differing profiles of typical (first generation) and atypical (second generation) antipsychotics adding to a confusing array of terminology and dilemma of what is the best medication for service users.

Searches

This review investigates the effects of different antipsychotic combinations compared with single antipsychotics for people with schizophrenia. Searches for randomised controlled trials have now been run by the Information Specialist of the Cochrane Schizophenia Group in 2010, 2012 and 2016. Sixty-two trials, reporting useable data, are included in the review.

Main results

The review of available evidence found that combinations of antipsychotics may be more effective in treating symptoms of schizophrenia compared with taking one antipsychotic. In particular, combination treatments that included clozapine and typical antipsychotic in both groups were found to be effective. Few studies reported on this central issue of relapse rates (service users becoming unwell again), but this was because most of the studies were of short length (whereas schizophrenia is a long-term health problem that requires studies of an equally long duration). No real differences were found between combinations of antipsychotics and single antipsychotics for preventing relapse and roughly equal numbers of people discontinued their treatment. There was also no difference between combination therapy and monotherapy regarding hospital admission and/or occurrence of serious adverse events. Numbers leaving the studies early were similar. Clinically meaningful data for quality of life were not reported.

Conclusions

These results show that there may be some clinical benefit for combination therapy in that more people receiving a combination of antipsychotic showed an improvement in symptoms. For other important outcomes such as relapse, hospitalisation, adverse events, discontinuing treatment or leaving the study early, no clear differences between the two treatment options were observed. However, these results are based on very low or low-quality evidence and more research providing high-quality evidence is needed before firm conclusions can be made.

This plain language summary has been adapted from an original summary by Benjamin Gray, Service User and Service User Expert, Rethink Mental Illness. Email: ben.gray@rethink.org

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Combinations of antipsychotic drugs compared to single antipsychotic drugs for schizophrenia

Combinations of antipsychotic drugs compared to single antipsychotic drugs for schizophrenia

Patient or population: schizophrenia or related disorders
Setting: outpatients and inpatients
Intervention: combinations of antipsychotic drugs
Comparison: single antipsychotic drugs

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with single antipsychotic drugs	Risk with combinations of antipsychotic drugs				
Clinical response: No clinically important response - as defined by each of the studies follow up: range 4 weeks to 52 weeks	Study population		RR 0.73 (0.64 to 0.83)	2398 (29 RCTs)	⊕⊖⊖⊖ VERY LOW [1 2 3 4]	
	512 per 1,000	374 per 1,000 (328 to 425)				
Relapse - as defined by each of the studies follow up: range 2 months to 36	Study population		-	512 (3 RCTs)	-	Data were not pooled due to high heterogeneity (I^2 = 82%). Two studies showed no difference between the interventions and one study favoured antipsychotic combinations.
	see comment	see comment				
Leaving the study early follow up: range 6 weeks to 52 weeks	Study population		RR 0.90 (0.76 to 1.07)	3137 (43 RCTs)	⊕⊕⊖⊖ LOW [2 5 7]	
	183 per 1,000	164 per 1,000 (139 to 195)				
Service utilisation: Hospital admission follow up: range 12 weeks to 26 weeks	Study population		RR 0.96 (0.36 to 2.55)	202 (3 RCTs)	⊕⊖⊖⊖ VERY LOW [2 5 6]	
	69 per 1,000	67 per 1,000 (25 to 177)				
Service utilisation: Change in hospital status - not reported	Study population		not estimable	(studies)	-	No studies provided data for this outcome.

	0 per 1,000	0 per 1,000 (0 to 0)				
Adverse events: Serious event or requiring discontinuation follow up: range 6 weeks to 8 months	Study population		RR 1.05 (0.65 to 1.69)	2398 (30 RCTs)	⊕⊖⊖⊖ VERY LOW [1 2 5 7]	
	47 per 1,000	49 per 1,000 (31 to 80)				
Quality of life assessed with: QLS, SWN and SF-36 follow up: range 6 weeks to 16	see comment	see comment	-	398 (4 RCTs)	-	Data were not pooled, as they were presented in both change and endpoint data for 3 different scales. None of the scales showed a difference between the two groups.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded one level due to risk of bias.
[2] Downgraded one level due to inconsistency.
[3] Although there is a concern about the timeframe to measure the outcome we decided not to downgrade due to overall quality assessment.
[4] Downgraded one level due to publication bias.
[5] Downgraded one level due to imprecision.
[6] Downgraded one level due to indirectness.
[7] Although there is a concern about the influence on industry we decided not to downgrade due to overall quality assessment.
[8] Downgraded two levels due to inconsistency.
Please see Checklist to aid consistency and reproducibility of GRADE assessments Appendix 1.

BACKGROUND

Description of the condition

Schizophrenia is a chronic disorder with a lifetime prevalence of four per 1000 persons (McGrath 2008). It is characterised by emotional, cognitive, and behavioural dysfunctions. In order to meet the diagnostic criteria of schizophrenia, patients require two or more positive, disorganised, or negative symptoms that persist for at least six months, with at least one of them being a positive symptom or disorganised speech (APA 2013). Positive symptoms include delusions (e.g. a false belief that is resistant to change, immune to contradictory evidence, and without correlation to the sociocultural background) and hallucinations (e.g. a sensory experience in the absence of external stimulus to the corresponding sensory organ). Negative symptoms are characterised by deficits in normal behaviour, which consist of five domains: blunted affect, alogia, asociality, anhedonia, and avolition (Kirkpatrick 2006).

Schizophrenia is difficult to treat and significantly burdens an individual's daily life. Despite the introduction of antipsychotics in the 1950s and the reintroduction of clozapine to the Western world, the mean recovery rate of schizophrenia is 13.5% (Jääskeläinen 2012). In clinical practice, multiple augmentation strategies such as adding another antipsychotic, mood-stabiliser, benzodiazepines, lithium, electroconvulsive therapy, or repetitive transcranial magnetic stimulation have been used for these patients in order to improve their clinical state, but the evidence for the use of these interventions is lacking (Hasan 2012).

Description of the intervention

Antipsychotic medications are the cornerstone for the treatment of schizophrenia. They were originally classified on the basis of their risk for the development of extrapyramidal side effects (EPS) as typical (e.g. chlorpromazine, haloperidol, fluphenazine) or atypical (e.g. clozapine, olanzapine, risperidone) if the risk for the development of EPS is low (Grunder 2009).

Antipsychotic polypharmacy/combination treatment, e.g. concurrent treatment with more than one antipsychotic medication, is a common strategy for the management of disturbed behaviour, poor response to antipsychotic monotherapy, or acute positive symptom exacerbation (Paton 2008). Concerning this practice, recommendations are varied. While some countries justify this practice (e.g. Finland, France, the UK), others recommend against it (e.g. Canada, Denmark, Spain), and many abstain from making any recommendation (Gaebel 2005). Regardless of the recommendations and lack of evidence, this practice has shown a trend towards increased use over time (Gangluy 2004). It is estimated that 19.6% of patients with schizophrenia across the world receive antipsychotic polypharmacy/combination treatment (Gallego 2009).

How the intervention might work

Currently, there is not a current understanding of how the combination of antipsychotics might work. Plausible hypotheses include (Freudenreich 2002):

1. achieving optimal receptor occupancy;
2. targeting different receptors with the added drug (Kapur 2001); and
3. reducing the dose-related side-effects by using lower doses of the two drugs.

Why it is important to do this review

A number of potential concerns regarding antipsychotic combinations have been identified. These include the possibility of unnecessarily high doses, an increased acute and/or chronic side-effect burden, adverse pharmacodynamic and pharmacokinetic interactions, increased rates of non-compliance, difficulties in determining cause and effect of multiple treatments, potential increased mortality, higher costs and poorly documented risks and benefits of this practice (Centorrino 2005; Meltzer 2000; Misawa 2011; Rupnow 2007; Waddington 1998; Weiden 1999). In this review, we examine the evidence for the efficacy and safety of antipsychotic combinations in the treatment of schizophrenia and schizophrenia-like psychoses. We are aware of the sister Cochrane review investigating the effects of different clozapine-antipsychotic combinations (Barber 2017). However, this review is different in its scope as it investigates any combinations of antipsychotic therapy versus any antipsychotic monotherapy.

OBJECTIVES

To examine whether:

1. treatment with antipsychotic combinations is effective for schizophrenia; and
2. treatment with antipsychotic combinations is safe for the same illness.

METHODS

Criteria for considering studies for this review

Types of studies

We included all relevant randomised controlled trials (RCTs) and quasi-RCTs. Where a trial was described as 'double-blind' and it implied that the study was randomised and the demographic details of each group were similar, those trials were also included. After debate we decided to maintain the same inclusion criteria determined by previous authors to include quasi-RCTs (see Differences between protocol and review).

Types of participants

Adults, however defined, with schizophrenia or related disorders, including schizophreniform disorder, schizoaffective disorder and delusional disorder, again, by any means of diagnosis.

Types of interventions

1. Treatment with more than one antipsychotic medication

Any dose and route of administration.

2. Treatment with only one antipsychotic medication

Any dose and route of administration.

Types of outcome measures

We grouped outcomes into long term (over 26 weeks, A), medium term (13 to 26 weeks, B) and short term (up to 12 weeks, C).

Primary outcomes

1. Clinical response

1.1 No clinically important response - as defined by each of the studies

1.2 Relapse - as defined by each of the studies

2. Leaving the study early

Secondary outcomes

1. Service utilisation

1.1 Hospital admission
1.2 Days in hospital
1.3 Change in hospital status

2. Clinical response

2.1 No clinically important improvement of global state
2.2 Average score/change in global state
2.3 No clinically important improvement in mental state - as defined by each of the studies
2.4 Average score/change in mental state
2.5 No clinically important response on positive symptoms - as defined by each of the studies
2.6 Average score/change in positive symptoms
2.7 No clinically important response on negative symptoms - as defined by each of the studies
2.8 Average score/change in negative symptoms
2.9 No clinically important response on aggression/agitation symptoms - as defined by each of the studies
2.10 Average score/change in aggression/agitation symptoms

3. Behaviour

3.1 General behaviour
3.2 Specific behaviours
3.2.1 Social functioning
3.2.2 Employment status during trial (employed / unemployed)
3.2.3 Occurrence of violent incidents (to self, others, or property)
3.2.4 Level of substance abuse

4. Adverse events

4.1 Serious adverse events
4.2 Adverse events requiring hospitalisation
4.3 Specific adverse events
4.3.1 Allergic reactions
4.3.2 Blood dyscrasia such as agranulocytosis
4.3.3 Central nervous system (ataxia, nystagmus, drowsiness, fits, diplopia, tremor)
4.3.4 Death (suicide and non-suicide deaths)
4.3.5 Endocrinological dysfunction (hyperprolactinaemia)
4.3.6 Weight gain
4.3.7 Movement disorders (extrapyramidal side effects (EPS))

5. Quality of life

6. Economic burden (cost of care)

'Summary of findings' table

We used the GRADE approach to interpret findings (Schünemann 2011), and used GRADE profiler (GRADEPRO) to import data from RevMan 5 (Review Manager) in order to create a 'Summary of findings' table. This table provides outcome-specific information concerning the overall quality of evidence from each included study in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on all outcomes we rated as important to patient care and decision-making. Also, we prepared an appendix (Appendix 1) to help with the standardisation of the 'Summary of findings' table (please see Differences between protocol and review). We aimed to select the following main outcomes for inclusion in the 'Summary of findings' table.

1. Clinical response

1.1 No clinically important response - as defined by each of the studies

1.2 Relapse - as defined by each of the studies

2. Leaving the study early

3. Service utilisation

3.1 Hospital admission
3.2 Change in hospital status

4. Adverse events: clinically important - as defined by individual studies*

5. Quality of life: clinically important response - as defined by individual studies*

Search methods for identification of studies

Electronic searches

Cochrane Schizophrenia Group's Trials Register

The Information Specialist searched the Cochrane Schizophrenia Group's Study-Based Register of Trials (June 2010, August 2012 and 25 January, 2016) using the following search strategy, which has been developed based on literature review and consulting with the authors of the review:

(((antipsychot* or neuroleptic* or drug*) and combin*) or *add-on* or *addition*or *supplement*or *supplementation*or *cotreatment*or *co-treatment*or *adjunctive* or *concurrent* or *concomitant* or *simultaneous* or *parallel* or *polypharmacy) in title, abstract or index terms of REFERENCE or (*polytherapy* or *augmentation* or *parallel* or *combined*) in interventions of STUDY

In such a study-based register, searching the major concept retrieves all the synonym keywords and relevant studies because all the studies have already been organised based on their interventions and linked to the relevant topics.

The Cochrane Schizophrenia Group's Register of Trials is compiled by systematic searches of major resources (including AMED, BIOSIS, CINAHL, Embase, MEDLINE, PsycINFO, PubMed, and registries of clinical trials) and their monthly updates, handsearches, grey literature, and conference proceedings (see Group's Module). There is no language, date, document type, or publication status limitations for inclusion of records into the register.

Searching other resources

1. Reference searching

We inspected references of all included studies for further relevant studies.

2. Personal contact

Where necessary, we contacted the first author of each included study for information regarding unpublished trials. We noted the outcome of this contact in the Characteristics of included studies, Characteristics of studies awaiting classification tables.

Data collection and analysis

The text below describes data collection and analysis for the 2016 search; the previous data collection and analysis can be seen in Appendix 2.

Selection of studies

Two review authors JO and SC inspected all abstracts of studies identified as above and identified potentially relevant reports. YH screened the Chinese language studies, and one study in Korean language was inspected by HH. We resolved disagreements by discussion, or where there was still doubt, we acquired the full-text article for further inspection. We acquired the full-text articles of relevant reports/abstracts meeting initial criteria for reassessment and carefully inspected for a final decision on inclusion (see Criteria for considering studies for this review). JO and SC were not blinded to the names of the authors, institutions or journal of publication. Where difficulties or disputes arose, we asked author LC for help, and where it was impossible to decide or if adequate information was not available to make a decision, we added these studies to those awaiting assessment and contacted the authors of the papers for clarification.

Data extraction and management

1. Extraction

Review authors JO and SC independently extracted data from all included studies and YH extracted data for Chinese studies. In addition, to ensure reliability, LC extracted data from a random sample of these studies, comprising 10% of the total. Again, we discussed any disagreement and documented decisions. With any remaining problems, LC helped clarify issues and we documented these final decisions. We extracted data presented only in graphs and figures whenever possible, but included only if two review authors independently had the same result. We attempted to contact authors through an open-ended request in order to obtain missing information or for clarification whenever necessary. If studies were multi-centre, where possible, we extracted data relevant to each component centre separately.

2. Management

2.1 Forms

We adapted the 'Data collection form for intervention reviews' provided by Cochrane to collect data.

2.2 Scale-derived data

We included continuous data from rating scales only if:

a) the psychometric properties of the measuring instrument have been described in a peer-reviewed journal (Marshall 2000); and
b) the measuring instrument has not been written or modified by one of the trialists for that particular trial.

Ideally, the measuring instrument should either be: i. a self-report or ii. completed by an independent rater or relative (not the therapist). We realise that this is not often reported clearly, therefore we noted in Description of studies if this was the case or not.

2.3 Endpoint versus change data

There are advantages of both endpoint and change data. Change data can remove a component of between-person variability from the analysis. On the other hand, calculation of change needs two assessments (baseline and endpoint), which can be difficult in unstable and difficult to measure conditions such as schizophrenia. We decided primarily to use endpoint data, and only use change data if the former were not available. We did not combined endpoint data and change data, we decided to present the data in the analysis separately (see Differences between protocol and review).

2.4 Skewed data

Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we applied the following standards to relevant data before inclusion.

Please note, we entered data from studies of at least 200 participants in the analysis irrespective of the following rules, because skewed data pose less of a problem in large studies. We also entered all relevant change data, as when continuous data are presented on a scale that includes a possibility of negative values (such as change data), it is difficult to tell whether data are skewed or not.

For endpoint data:

(a) when a scale started from the finite number zero, we subtracted the lowest possible value from the mean, and divided this by the standard deviation (SD). If this value was lower than 1, it strongly suggests a skew and we excluded these data. If this ratio was higher than one but below 2, there is suggestion of skew. We entered these data and tested whether their inclusion or exclusion changed the results substantially. Finally, if the ratio was larger than 2 we included these data, because skew is less likely (Altman 1996; Higgins 2011).

(b) if a scale starts from a positive value (such as the Positive and Negative Syndrome Scale (PANSS), (Kay 1986)) which can have values from 30 to 210), we modified the calculation described above to take the scale starting point into account. In these cases skew is present if 2 SD > (S-S min), where S is the mean score and 'S min' is the minimum score.

2.5 Common measure

Where relevant, to facilitate comparison between trials, we converted variables that can be reported in different metrics, such as days in hospital (mean days per year, per week or per month) to a common metric (e.g. mean days per month).

2.6 Conversion of continuous to binary

Where possible, we converted continuous outcome measures to dichotomous data. This can be done by identifying cut-off points on rating scales and dividing participants accordingly into 'clinically improved' or 'not clinically improved'. It is generally assumed that if there is a 50% reduction in a scale-derived score such as the Brief Psychiatric Rating Scale (BPRS, Overall 1962), or the Positive and

Negative Syndrome Scale (PANSS, Kay 1986), this can be considered as a clinically significant response (Leucht 2005; Leucht 2005a). If data based on these thresholds were not available, we used the primary cut-off presented by the original authors.

2.7 Direction of graphs

Where possible, we entered data in such a way that the area to the left of the line of no effect indicated a favourable outcome for treatment with antipsychotic combinations. Where keeping to this made it impossible to avoid outcome titles with clumsy double-negatives (e.g. 'Not un-improved'), we presented data where the left of the line indicates an unfavourable outcome and noted this in the relevant graphs.

Assessment of risk of bias in included studies

Review authors, JO and SC independently assessed the risk of bias of each trial published in English and YH assessed trials published in Chinese by using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess trial quality (Higgins 2011a). This set of criteria is based on evidence of associations between overestimate of effect and high risk of bias of the article such as sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting.

If the raters disagreed, we made the final rating by consensus, with the involvement of LC. Where inadequate details of randomisation and other characteristics of trials were provided, we contacted authors of the studies in order to obtain further information. If non-concurrence occurred, we reported this.

We noted the level of risk of bias in the text of the review and in Figure 1, Figure 2 and Summary of findings for the main comparison.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

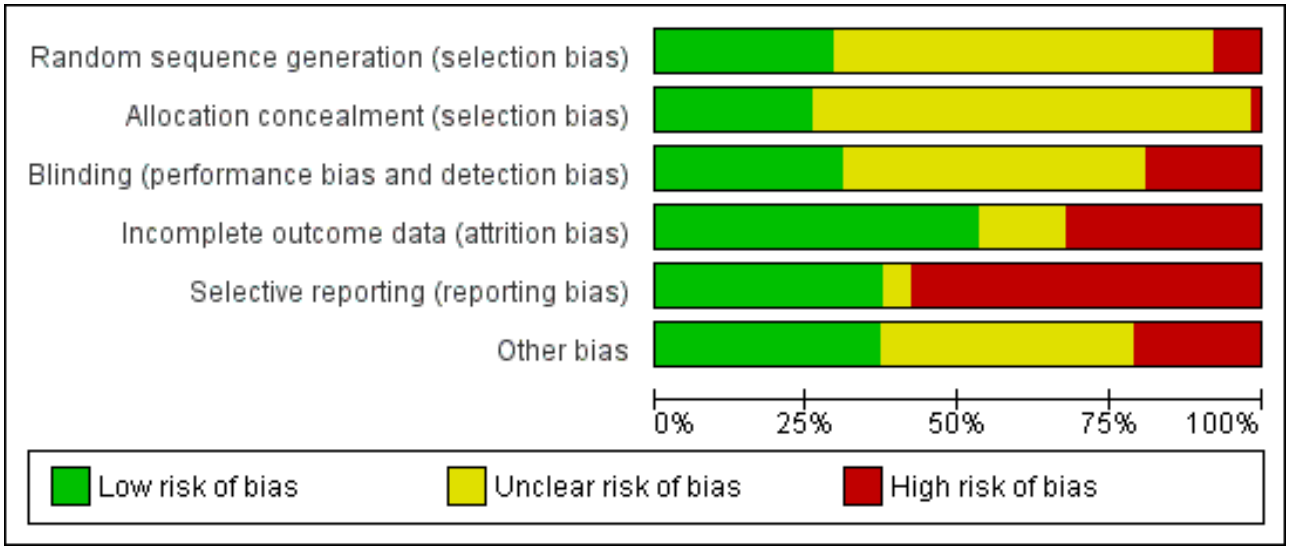


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

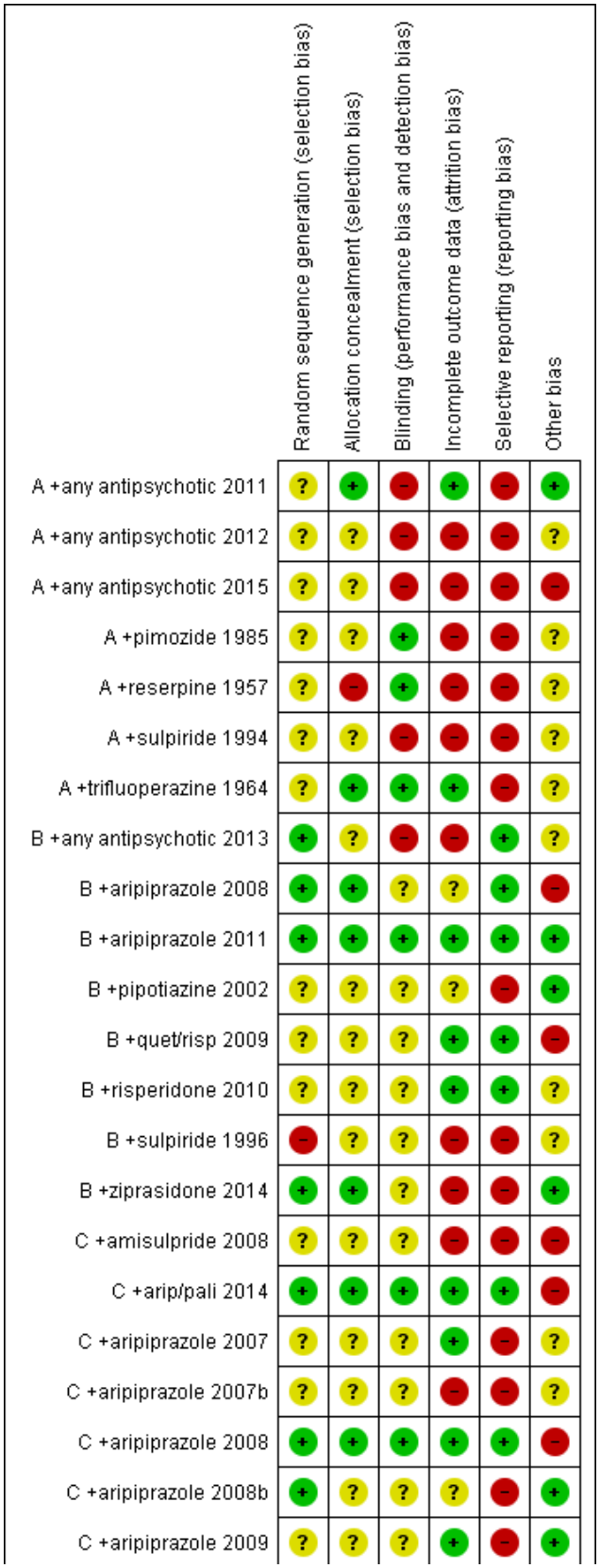


Figure 2. (Continued)

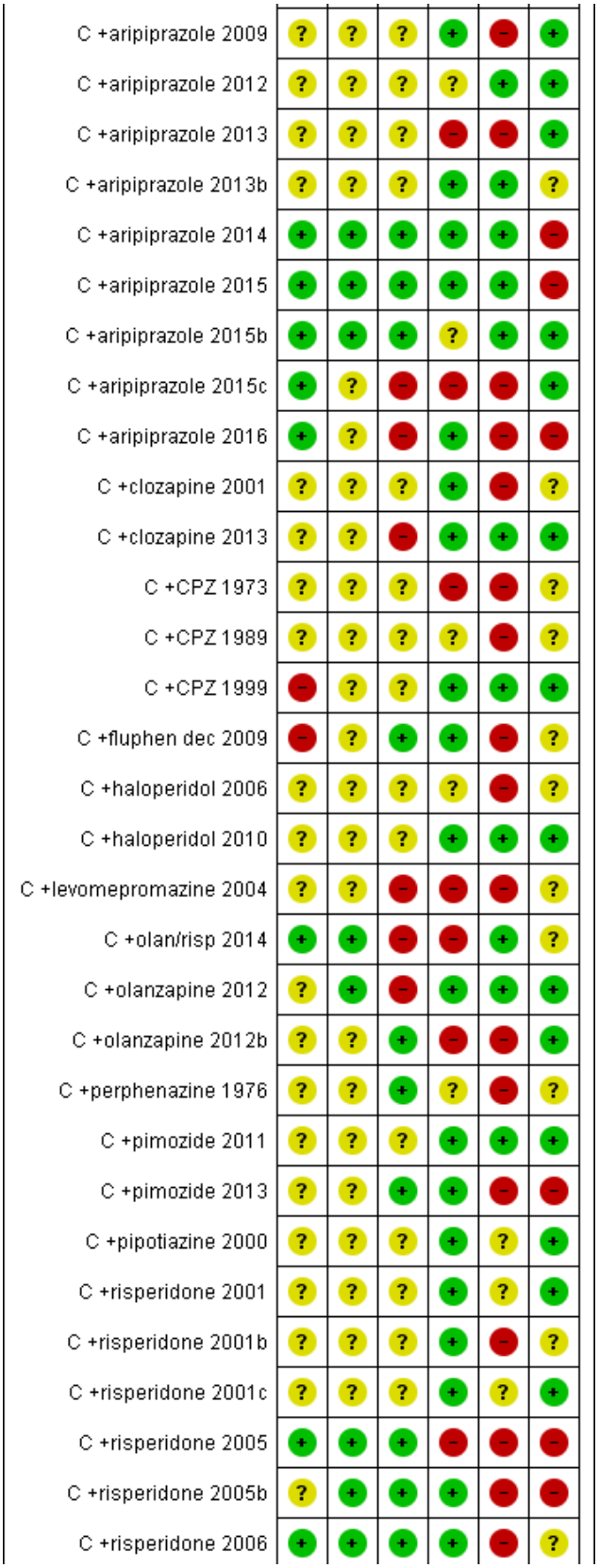
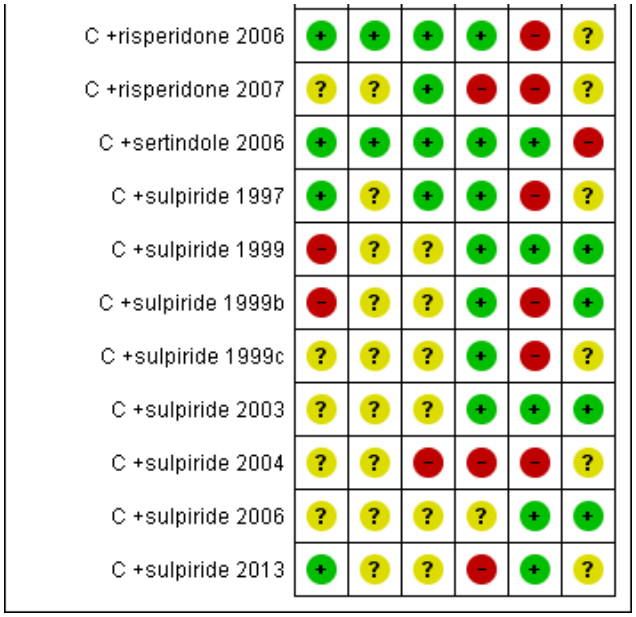


Figure 2. (Continued)



Measures of treatment effect

1. Binary data

For binary outcomes, we calculated a standard estimation of the risk ratio (RR) and its 95% confidence interval (CI). It has been shown that RR is more intuitive (Boissel 1999) than odds ratios and that odds ratios tend to be interpreted as RR by clinicians (Deeks 2000).

2. Continuous data

For continuous outcomes, we estimated mean difference (MD) between groups. We preferred not to calculate effect size measures (standardised mean difference (SMD)). However, if scales of very considerable similarity were used, we presumed there was a small difference in measurement, and calculated the effect size and transformed the effect back to the units of one or more of the specific instruments.

Unit of analysis issues

1. Cluster trials

Studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice), but analysis and pooling of clustered data poses problems. Firstly, authors often fail to account for intra-class correlation in clustered studies, leading to a 'unit of analysis' error (Divine 1992), whereby P values are spuriously low, confidence intervals unduly narrow and statistical significance overestimated. This causes type I errors (Bland 1997; Gulliford 1999).

Where clustering was not accounted for in primary studies, we presented such data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. In subsequent versions of this review we will seek to contact first authors of studies to obtain intra-class correlation coefficients (ICCs) for their clustered data and to adjust for this by using accepted methods (Gulliford 1999). Where clustering has been incorporated into the analysis of primary studies, we will present these data as if from a non-cluster randomised study, but adjust for the clustering effect.

We have sought statistical advice and have been advised that the binary data as presented in a report should be divided by a 'design effect'. This is calculated using the mean number of participants per cluster (Bm) and the ICC [Design effect = 1+(m-1)*ICC] (Donner 2002). If the ICC is not reported it will be assumed to be 0.1 (Ukoumunne 1999).

If cluster studies have been appropriately analysed taking into account ICCs and relevant data documented in the report, synthesis with other studies would be possible using the generic inverse variance technique.

2. Cross-over trials

A major concern of cross-over trials is the carry-over effect. It occurs if an effect (e.g. pharmacological, physiological or psychological) of the treatment in the first phase is carried over to the second phase. As a consequence, on entry to the second phase the participants can differ systematically from their initial state despite a wash-out phase. For the same reason cross-over trials are not appropriate if the condition of interest is unstable (Elbourne 2002). As both effects are very likely in severe mental illness, we only used data from the first phase of cross-over studies.

3. Studies with multiple treatment groups

Where a study involved more than two treatment arms, if relevant, we presented the additional treatment arms in comparisons. If data were binary, we simply added and combined within the two-by-two table. If data were continuous, we combined data following the formula in section 7.7.3.8 (Combining groups) of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We did not use data where the additional treatment arms were not relevant.

Dealing with missing data

1. Overall loss of credibility

At some degree of loss of follow-up, data must lose credibility (Xia 2009). We chose that, for any particular outcome, should more than 50% of data be unaccounted for, we would not reproduce these data or use them within analyses. If, however, more than 50% of those in one arm of a study were lost, but the total loss was less than 50%, we addressed this within the 'Summary of findings' table by down-rating quality. We also downgraded quality within the 'Summary of findings' table should loss be 25% to 50% in total.

2. Binary

In the case where attrition for a binary outcome was between 0% and 50% and where these data were not clearly described, we presented data on a 'once-randomised-always-analyse' basis (an intention-to-treat (ITT) analysis). We assumed all those leaving the study early to have the same rates of negative outcome as those who completed -except for the outcomes of death and adverse effects- for these outcomes we used the rate of those who stayed in the study (in that particular arm of the trial) for those who did not. We undertook a sensitivity analysis to test how prone the primary outcomes were to change by comparing data only from people who completed the study to that point to the ITT analysis using the above assumptions.

3. Continuous

3.1 Attrition

We reported and used data where attrition for a continuous outcome was between 0% and 50%, and data only from people who completed the study to that point were reported.

3.2 Standard deviations

If standard deviations (SDs) were not reported, we first tried to obtain the missing values from the authors. If not available, where there were missing measures of variance for continuous data, but an exact standard error (SE) and confidence intervals available for group means, and either P value or T value available for differences in mean, we calculated them according to the rules described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). When only the SE is reported, SDs) are calculated by the formula SD = SE * square root (N). Chapters 7.7.3 and 16.1.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011) present detailed formulae for estimating SDs from P values, t or F values, confidence intervals, ranges or other statistics. If these formulae did not apply, we calculated the SDs according to a validated imputation method, which is based on the SDs of the other included studies (Furukawa 2006). Although some of these imputation strategies can introduce error, the alternative would be to exclude a given study's outcome and thus to lose information. We nevertheless examined the validity of the imputations in a sensitivity analysis excluding imputed values.

3.3 Assumptions about participants who left the trials early or were lost to follow-up

Various methods are available to account for participants who left the trials early or were lost to follow-up. Some trials just present the results of study completers, others use the method of last observation carried forward (LOCF), while more recently methods such as multiple imputation or mixed-effects models for repeated measurements (MMRM) have become more of a standard. While the latter methods seem to be somewhat better than LOCF (Leon 2006), we feel that the high percentage of participants leaving the studies early and differences in the reasons for leaving the studies early between groups is often the core problem in randomised schizophrenia trials. We therefore did not exclude studies based on the statistical approach used. However, we preferred to use the more sophisticated approaches. (e.g. MMRM or multiple-imputation) and only presented completer analyses if some kind of ITT data were not available at all. Moreover, we addressed this issue in the item "incomplete outcome data" of the 'Risk of bias' tool.

Assessment of heterogeneity

1. Clinical heterogeneity

We considered all included studies initially, without seeing comparison data, to judge clinical heterogeneity. We simply inspected all studies for clearly outlying people or situations which we had not predicted would arise and discussed in the text if they arose.

2. Methodological heterogeneity

We considered all included studies initially, without seeing comparison data, to judge methodological heterogeneity. We simply inspected all studies for clearly outlying methods which we had not predicted would arise and discussed in the text if they arose.

3. Statistical heterogeneity

3.1 Visual inspection

We visually inspected graphs to investigate the possibility of statistical heterogeneity.

3.2 Employing the I^2 statistic

We investigated heterogeneity between studies by considering the I^2 method alongside the Chi^2 P value. The I^2 provides an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of I^2 depends on i. magnitude and direction of effects and ii. strength of evidence for heterogeneity (e.g. P value from Chi^2 test, or a confidence interval for I^2). An I^2 estimate greater than or equal to around 50% accompanied by a statistically significant Chi^2 statistic, can be interpreted as evidence of substantial levels of heterogeneity (Section 9.5.2 - Deeks 2011). We explored and discussed in the text potential reasons for substantial levels of heterogeneity (Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). These are described in Section 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2011). We are aware that funnel plots may be useful in investigating reporting biases but are of limited power to detect small-study effects. We did not use funnel plots for outcomes where there are 10 or fewer studies, or where all studies were of similar sizes. In future versions of this review, if funnel plots are possible, we will seek statistical advice in their interpretation.

Data synthesis

We understand that there is no closed argument for preference for use of fixed-effect or random-effects models. The random-effects method incorporates an assumption that the different studies are estimating different, yet related, intervention effects. This often seems to be true to us and the random-effects model takes into account differences between studies even if there is no statistically significant heterogeneity. There is, however, a disadvantage to the random-effects model. It puts added weight onto small studies which often are the most biased ones. Depending on the direction of effect, these studies can either inflate or deflate the effect size. We chose random-effects model for all analyses.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

We presented data in the analyses grouped by the type of antipsychotic used: trials with clozapine in both the monotherapy and combination arm, trials with other atypical drugs in both the monotherapy and combination arms, trials with typical antipsychotic drugs in both arms, or any antipsychotics in both groups, in order to facilitate subgroup analyses (see Differences between protocol and review).

1.1 Primary outcomes

In addition, we also undertook subgroup analyses comparing the results for the following:

1. enrolment of acutely exacerbated or chronically ill patients;
2. treatment duration <12 weeks vs ≥12 weeks;
3. clozapine vs non-clozapine combinations; and
4. drug added to clozapine treatment.

2. Investigation of heterogeneity

If inconsistency was high first, we investigated whether data were entered correctly. Second, if data were correct, we visually inspected the graph and successively removed outlying studies to see if homogeneity was restored. For this review, we decided that should this occur with data contributing to the summary finding of no more than around 10% of the total weighting, we would present data. If not, we would not pool such data but discuss issues. We know of no supporting research for this 10% cut-off but are investigating use of prediction intervals as an alternative to this unsatisfactory state.

We performed a meta-regression for the primary outcome 'No clinically important response' (Please see Differences between protocol and review).

When unanticipated clinical or methodological heterogeneity were obvious, we simply discussed these. We did not undertake sensitivity analyses relating to these.

Sensitivity analysis

1. Implication of randomisation

If trials were described in some way as to imply randomisation, we undertook a sensitivity analyses for the primary outcomes. We included these studies in the analyses and if there was no substantive difference when the implied randomised studies were added to those with better description of randomisation, then we used relevant data from these studies.

2. Assumptions for lost binary data

Where assumptions had to be made regarding people lost to follow-up (see Dealing with missing data), we compared the findings of the primary outcomes when we used our assumption compared with completer data only. If there was a substantial difference, we reported and discussed these results, but continued to employ our assumption.

Where assumptions had to be made regarding missing SDs data (see Dealing with missing data), we compared the findings of the primary outcomes when we used our assumption compared with completer data only. We undertook a sensitivity analysis to test how prone results were to change when 'completer' data only were compared to the imputed data using the above assumption. If there was a substantial difference, we reported and discussed these results, but continued to employ our assumption.

3. Risk of bias

We analysed the effects of excluding trials that we judged to be at high risk of bias across one or more of the domains of randomisation (implied as randomised with no further details available) allocation concealment, blinding and outcome reporting for the meta-analysis of the primary outcome. If the exclusion of trials at high risk of bias did not substantially alter the direction of effect or the precision of the effect estimates, we included data from these trials in the analysis

4. Imputed values

We undertook a sensitivity analysis to assess the effects of including data from trials where we used imputed values for ICCs in calculating the design effect in cluster-randomised trials.

If we found substantial differences in the direction or precision of effect estimates in any of the sensitivity analyses listed above, we did not pool data from the excluded trials with the other trials contributing to the outcome, but presented them separately

5. Fixed and random effects

We synthesised data using a random-effects model, however, we also synthesised data for the primary outcome using a fixed-effect model to evaluate whether this altered the significance of the results

RESULTS

Description of studies

Please also see Characteristics of included studies, Characteristics of excluded studies, Characteristics of studies awaiting classification, and Characteristics of ongoing studies. To try and aid clarity, we have named the studies in an unusual manner. The study tag starts with the duration category (A = long term (over 26 weeks); B = medium term (13 to 26 weeks) and C = short term (up to 12 weeks); the remainder of the tag is the additional drug in the combination antipsychotic group (chlorpromazine has to be shortened to 'CPZ'). Finally, if two studies had similar names an alphabetical tag (- b, - c) was added.

Results of the search

Searches were originally carried out in 2010 and 2012. We supplemented these with a January 2016 search of the Cochrane Schizophrenia Group's Register of trials. Another trial (Xu 2006) was added as it appeared as a reference in one of the included trials (C +aripiprazole 2014). We included one trial (C +aripiprazole 2015b) that was found by methods not described in the protocol (please see Differences between protocol and review). From these searches 62 trials met the inclusion criteria. Sixty-two trials were excluded. There are three trials awaiting assessment (Characteristics of studies awaiting classification) and there are three ongoing studies (Figure 3).

Figure 3. Naming of the subgroups: The studies were arranged into four subgroups according to the type of antipsychotics used in both arms: clozapine, atypical antipsychotics other than clozapine, typical antipsychotics and any antipsychotics. Naming of the studies: The study tag starts with the duration category (A = long term (over

26 weeks); B = medium term (13 to 26 weeks) and C = short term (up to 12 weeks); the remainder of the tag is the additional drug in the combination antipsychotic group.

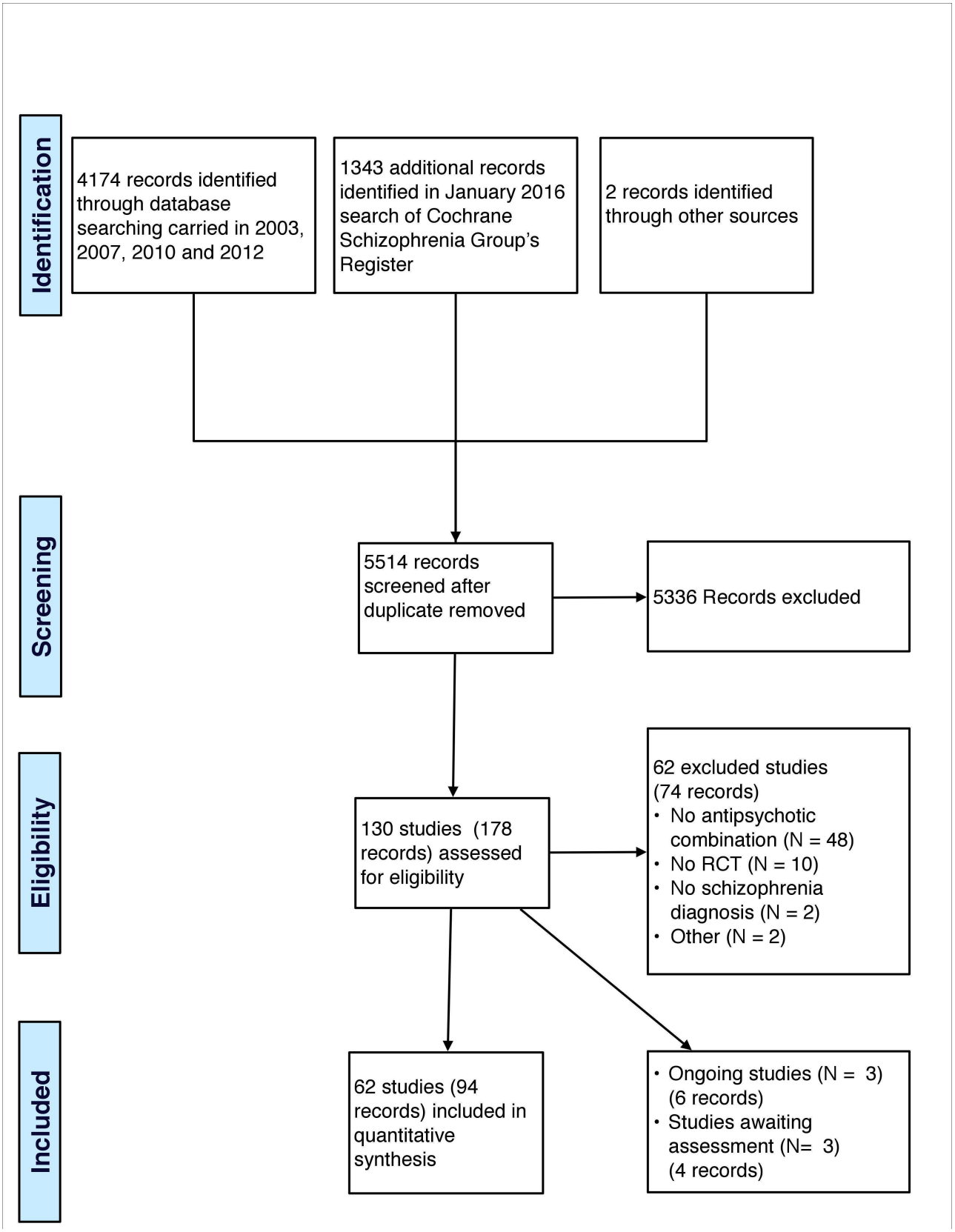


Figure 3. (Continued)

Included studies

The current review includes 94 reports describing 62 trials (4833 participants); 41 studies were two-arm trials comparing an antipsychotic monotherapy with a combination therapy; 12 trials were three-arm studies comparing two monotherapies with the combination therapy; four were three-arm trials comparing one monotherapy with two combinations, and three studies were four-arm trials comparing two monotherapies with two combinations. C +aripiprazole 2015 was a four-arm trial comparing one combination therapy at three different doses against monotherapy, and, finally, A +pimozide 1985 was an eight-arm trial comparing two monotherapies at two different doses with one combination therapy at four different doses.

1. Study duration

Forty-seven of the included studies were short term in duration (less than 12 weeks, C). Eight were of medium term (13 to 26 weeks, B) and seven were long term (over 26 weeks, A).

2. Design

Most of the included studies presented a parallel longitudinal design. However A +reserpine 1957 and C +olanzapine 2012b, were cross-over trials and we only used data from the first phase of these trials until the point of the first cross-over. Nine were multi-centre trials; B +aripiprazole 2008 had centres across Europe and in South Africa, C +risperidone 2006 centres in Canada, Germany, China and the UK, and the other seven within their respective countries include (A +any antipsychotic 2011: USA; B +quet/risp 2009: USA; C +perphenazine 1976: Japan; C +aripiprazole 2013b: Korea; A +any antipsychotic 2015: USA; C +pimozide 2013: USA; C +olan/risp 2014; Japan).

3. Participants

A total of 4833 participants are included (average ˜78 people per study). C +haloperidol 2006 and A +any antipsychotic 2012 did not report the country of origin. See also Appendix 3.

All studies included people with schizophrenia, schizophreniform psychoses, delusional disorder and schizoaffective psychoses. Several means of diagnoses were used. See Appendix 4.

Most studies included people that had chronic schizophrenia and/or had experienced treatment failure while taking monotherapy antipsychotics. The average age was about 36 years old.

4. Settings

Thirty studies included inpatients, 16 studies included outpatients and seven studies both inpatients and outpatients. Two studies (C +aripiprazole 2009; C +sulpiride 1999) included participants in a community setting. Seven studies did not report the setting (C +aripiprazole 2007b, C +aripiprazole 2014, C +haloperidol 2006, C +pipotiazine 2000, C +sertindole 2006, C +sulpiride 1997, and C +sulpiride 2006).

5. Interventions

Full details of the doses used are reported in Characteristics of included studies and Appendix 5. We arranged the studies into four subgroups according to the type of antipsychotics used in both the monotherapy and combination group: clozapine, atypical antipsychotics other than clozapine, typical antipsychotics and any antipsychotics.

In order to determine if the doses used for the antipsychotics in the monotherapy groups were standard, we compared the dosages used in the clinical trials versus dosages suggested by Hasan 2012 and Gardner 2010. We decided not to appraise the interventions in the combination group since there is no evidence for the optimal regimen.

Clozapine in both groups

Thirty-one studies tested clozapine in both the monotherapy and combination arms of the trial. In 26 of these studies an atypical antipsychotic was added to clozapine in the combination therapy, and in five studies a typical antipsychotic was added to clozapine.

Three studies (B +risperidone 2010, C +olanzapine 2012b and C +risperidone 2005) and of the 31 clozapine studies did not report the doses used. One study (C +sulpiride 2006) used below-standard doses of clozapine in the monotherapy group. In 25 studies, standard doses of clozapine were used. C +pimozide 2013 reported blood levels and showed higher blood levels of clozapine in the combination group. All except two studies used only oral antipsychotics; B +pipotiazine 2002 and C +pipotiazine 2000 included oral clozapine and pipotiazine administered through muscle injection.

Other atypical antipsychotics in both groups

Eighteen studies tested atypical antipsychotics (other than clozapine) in both the monotherapy and combination therapy arms of the trial. In two of these trials, a typical antipsychotic was added to an atypical one in the combination therapy, and in the other 16 studies, the combination therapy consisted of two atypical antipsychotics. One study (C +clozapine 2013) did not report the doses used. The rest of the studies used a standard dose of the antipsychotic in the monotherapy group. All except one study used only oral antipsychotics; C +fluphen dec 2009 included oral olanzapine and fluphenazine decanoate administered through muscle injection.

Typical antipsychotic in both groups

Nine studies tested typical antipsychotics in both arms. In four of these trials, an atypical antipsychotic was added to the typical antipsychotic in the combination therapy, and in five studies, the combination therapy consisted of two typical antipsychotics. Three studies (C +aripiprazole 2007b; C +aripiprazole 2009; C +levomepromazine 2004) did not report the doses used. Regarding the monotherapy group, three studies used standard doses, two studies (A +pimozide 1985; C +perphenazine 1976) used below-standard doses, and one study (C +CPZ 1973) used above-standard doses. All except one study used only oral antipsychotics; C +CPZ 1973 included oral chlorpromazine and fluphenazine decanoate administered through muscle injection.

Any antipsychotic in both groups

Four trials are included in this subgroup. All except one study included participants already on any combination of antipsychotics who were randomised to monotherapy by discontinuation of one of their current antipsychotics and therefore included any combination of two antipsychotics in the combination arm and any one antipsychotic in the monotherapy arm. Doses were reported as haloperidol, chlorpromazine or olanzapine equivalent. Two trials used standard doses, one study (A +any antipsychotic 2015), used above-standard doses in both groups. A +any antipsychotic 2012 included participants treated with monotherapy who were randomised to switch to combination therapy by adding another antipsychotic or to continue receiving monotherapy. The medication to be added was decided by the prescriber and the patient; no doses were reported for this study.

6. Outcomes

The included studies provided data for the following outcomes: leaving the study early, clinical improvement, relapse, adverse events (serious or requiring discontinuation, death, movement disorders, prolactin level and weight gain), and used various scales to assess treatment effects in global state, mental state general and specific symptoms, movement disorders and quality of life.

6.1 Outcome scales

Only details of scales that provided usable data are shown below. Fifteen different instruments were used to collect scale data. Overall, scale data were poorly presented.

Global state

i. Clinical Global Impression Scale - CGI Scale (Guy 1976)
This is used to assess both severity of illness and clinical improvement, by comparing the conditions of the person standardised against other people with the same diagnosis. A seven-point scoring system is usually used with low scores showing decreased severity and/or overall improvement. CGI-Severity (CGI-S) is one component of the CGI, which rates illness severity and CGI-Improvement (CGI-I) rates improvement. High scores indicate a worse outcome.

ii. Global Assessment Scale of Functioning Scale (GAF) (APA 2000).
This is a modified version of the Global Assessment Scale (GAS) (Endicott 1976), an observer-rated scale for evaluating the overall functioning of a patient during a specified time period on a continuum from psychological or psychiatric sickness to health. Score ranges from zero to 100, where a higher score indicates a better outcome.

Mental state

i. Positive and Negative Syndrome Scale - PANSS (Kay 1987)
This schizophrenia scale has 30 items, each of which can be defined on a seven-point scoring system varying from one - absent to seven - extreme. This scale can be divided into three sub-scales for measuring the severity of general psychopathology, positive symptoms (PANSS-P), and negative symptoms (PANSS-N). A low score indicates lesser severity.

ii. Brief Psychiatric Rating Scale - BPRS (Overall 1962)
This is used to assess the severity of abnormal mental state. The original scale has 16 items, but a revised 18-item scale is commonly used. Each item is defined on a seven-point scale varying from 'not present' to 'extremely severe', scoring from zero to six or one to seven. Scores can range from zero to 126, with high scores indicating more severe symptoms.

iii. Scale for the Assessment of Positive Symptoms - SAPS (Andreasen 1984)
This six-point scale gives a global rating of positive symptoms such as delusions, hallucinations and disordered thinking. Higher scores indicate more symptoms.

iv.Scale for the Assessment of Negative Symptoms - SANS (Andreasen 1983)
This scale allows a global rating of the following negative symptoms: alogia (impoverished thinking), affective blunting, avolition-apathy, anhedonia-asociality, and attention impairment. Assessments are made on a six-point scale from zero (not at all) to five (severe). Higher scores indicate more symptoms.

Movement disorders

i. Barnes Akathisia Scale - BAS (Barnes 1989)
A scale consisting of four sub-scales to assess the severity of akathisia: objective rating (zero to three), subjective awareness of restlessness (zero to three), subjective distress related to restlessness (zero to three), and global clinical assessment of akathisia (zero to five). Higher scores indicate more severe akathisia.

ii. Abnormal Involuntary Movement Scale - AIMS (Guy 1976)
The AIMS is a 12-item scale consisting of a standardised examination followed by questions rating the orofacial, extremity and trunk movements, as well as three global measurements. Each of these 10 items can be scored from zero (none) to four (severe). Two additional items assess the dental status. The AIMS ranges from zero to 40, with higher scores indicating greater severity.

iii. Simpson Agnus Scale - SAS (Simpson 1970)
This scale contains 10 items: gait, arm dropping, shoulder shaking. elbow rigidity, wrist rigidity, leg pendulousness, head dropping, glabella tap, tremor and salivation. Each item is rated between zero and four. A total score is obtained by adding the items and dividing by 10. Scores of up to 0.3 are considered within the normal range. Higher scores indicate greater severity.

iv. Udvalg for Kliniske Undersøgelser Side Effect Rating Scale - UKU (Lingjaerde 1987)
A comprehensive, clinician-rated scale, designed to assess the side effects in patients treated with psychotropic medications. The UKU consists of 48 questions. Zero indicates normal; one indicates mild

symptoms; two indicates moderate symptoms; and three indicates severe symptoms. Higher scores indicate greater severity.

v. Drug-Induced Extrapyramidal Symptoms Scale - DIEPSS (Kim 2002)
The DIEPSS developed in Japan consists of four sub-scales for Parkinsonism (five items), akathisia, dystonia, and dyskinesia in combination with a global evaluation. Each item of assessment is rated on a five-point scale. The severity of each item is graded from zero (normal) to four (severe), higher scores indicate more severe symptoms.

vi. Extrapyramidal Symptom Rating Scale - ESRS (Chouinard 1980)
The ESRS measures movement disorders and scores range from zero to 246. There are sub-scales for parkinsonism (zero to 108), dystonia (zero to 96), and dyskinesia (zero to 42). Higher scores indicate more severe symptoms.

Quality of life

i. Quality of Life Scale - QLS (Heinrich 1984)
This six-point quality of life scale has been designed as an outcome instrument for schizophrenic deficit syndrome as well as to measure impaired functioning in studies of chronic schizophrenia, to assess the deficit syndrome's impact on the patient's life. There are seven severity steps (zero to six, six being adequately functioning and zero being deficient). The time frame is one month. Four item categories have been identified by factor analysis 1) interpersonal relationships (seven items), 2) instrumental role (four items), 3) intrapsychic function (seven items) and 4) commonplace objects and activities.

ii. Subjective well-being under neuroleptic treatment scale - SWN (Naber 1995)
This 38-item scale with five factors self-rating scale measures subjective well-being on neuroleptics. The 20 positively- and 18 negatively-phrased items are rated on a zero to five scale, from not at all, to very much. The five factors are 1) emotional regulation, 2) self-control, 3) mental functioning, 4) social integration and 5) physical functioning. Low scores predict non-compliance or discontinuation of treatment in maintenance periods.

iii. Short form-36 - SF-36 (Ware 1992)
This is a 36-item scale with two components, one measures the physical component and the other the mental component, the scores range from zero to 100. Each scale is subdivided in four factors. For the physical component: 1) physical functioning, 2) role-physical, 3) bodily pain, and 4) general health; and for the mental component: 1) vitality, 2) social functioning, 3) role-emotional, and 4) mental health. Lower scores indicate more disability.

Excluded studies

We excluded 62 studies from the review (Characteristics of excluded studies). Three trials (Barbui 2011, Zink 2009, JPRN-UMIN000017047) compared two combinations of antipsychotics but did not include a monotherapy. Wu 2015 compared two combinations of antipsychotics with the addition of a systematic nursing intervention. Eighteen studies were randomised control trials testing an antipsychotic combination, but the combinations did not include two antipsychotics. Twelve studies were randomised control trials comparing different antipsychotic monotherapies with another intervention. Seven studies were randomised control trials evaluating switching strategies to a different antipsychotic. Four trials (Sukegawa 2008, Sukegawa 2014, Yamanouchi 2015 and DRKS00008018) did not evaluate the combination of antipsychotics. Semenikhin 2013, NCT01939548 and NCT02477670 did not test antipsychotic drugs. Mantovani 2013 and Mythri 2013 did not evaluate participants with a diagnosis of schizophrenia. Ten studies were not randomised controlled trials. Henderson 2009 was a crossover trial that did not report the results separately for each phase. JPRN-UMIN000011710 ended without enrolling any patient.

1. Awaiting classification

There are three trials awaiting classification (Studies awaiting classification):

NCT01450514 is a clinical trial, which according to the principal investigator, enrolled patients but was concluded prematurely due to funding problems. We tried to obtain the data from the patients that started the trial, but the sponsor decided to keep the data confidential.

Xu 2006 is a clinical trial that evaluated the effects of aripiprazole compared with placebo on females with hyperprolactinaemia induced by antipsychotics. The placebo used for this trial was vitamin C (100 mg/day), which might have a significant effect on the symptoms of schizophrenia (Magalhães 2016).

Yuan 2014 is a clinical trial with multiple treatment stages. In the third stage, participants were able to receive a combinations of antipsychotics. We tried to obtain data regarding the participants who were enrolled on this stage but no response was received.

2. Ongoing studies

There are three ongoing studies (Characteristics of ongoing studies). One tests amisulpiride augmentation in clozapine-unresponsive schizophrenia (ISRCTN68824876), one olanzapine and amisulpiride (Schmidt-Kraepelin 2013), and one aripiprazole augmentation for participants with weight problems treated with clozapine (CTRI-02-003397).

Risk of bias in included studies

We prepared a 'Risk of bias' assessment for each trial. For multi-centre trials providing data for a single centre, we did not assess the risk of bias for each centre. Our judgments regarding the overall risk of bias in individual studies is illustrated in Figure 1 and Figure 2.

Allocation

Of the 62 trials analysed in this review, 18 reported an adequate generation of allocation sequence. In two studies (B +sulpiride 1996; C +fluphen dec 2009) the risk of bias was high for sequence generation as a quasi-randomised method was used, and three studies (C +CPZ 1999, C +sulpiride 1999, C +sulpiride 1999b) had a high risk of bias as they randomised according to hospital admission order or time. In all remaining studies, the method of assignment was unclear. Similarly, methods used to conceal allocation had a low risk of bias in 16 trials, high risk of bias in one and unclear in the remainder (please see Differences between protocol and review).

Blinding

In 19 studies, participants, care providers, and outcome assessors were blinded, 12 studies were high risk of bias for blinding as they were either open-label studies or the participants and personnel were not blinded; the risk of bias was unclear for the remaining 31 trials.

Incomplete outcome data

There was a low risk of bias for incomplete data in 33 studies, an unclear risk of bias in nine studies, and a high risk of bias in 20 trials.

Selective reporting

Twenty-three studies were free from selective reporting, 36 studies had a high risk of bias for selective reporting, and three had an unclear risk of bias.

Other potential sources of bias

Twenty-three studies were free from other biases, eight were subject to other biases and in the remaining studies the risk of bias was unclear.

Effects of interventions

See: **Summary of findings for the main comparison** Combinations of antipsychotic drugs compared to single antipsychotic drugs for schizophrenia

Where data were available, they were arranged into four subgroups according to the type of antipsychotics used in both arms: clozapine, atypical antipsychotics other than clozapine, typical antipsychotics and any antipsychotics. Studies were also named according to the add-on antipsychotic (see Description of studies), so it is possible to see in each analysis more information about the combination of antipsychotics used in each study, as well as the length of follow-up.

Where data were missing, such as standard deviations for continuous outcomes, we imputed these data using trials with similar means for that scale. We used the mean difference and reported the data separately for different scales within an outcome (Appendix 6).

For studies with more than two comparison groups we combined data, i.e. if the study tested different antipsychotics in two monotherapy groups or two combination groups. Where studies had two monotherapy groups, for studies with typical drugs in both groups data from the monotherapy groups were combined; for studies with clozapine in both groups, only data from the clozapine monotherapy group was added to the data analysis.

1. COMPARISON 1: ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY

This particular comparison has 63 outcomes.

1.1 Clinical response: 1. No clinically important response - not improved

We found twenty-nine trials (N = 2398), with six weeks to three years follow-up. We found that the use combination of antipsychotics may reducing the risk of no clinical response (RR 0.73 CI 0.64 to 0.83; Analysis 1.1; *very low quality evidence*). Results showed an important heterogeneity (I^2 = 54%). When we split the trials by length of follow-up, the results remain but there is no heterogeneity for the longer-term trials - the heterogeneity may be due to the short-term trials.

1.1.1 clozapine in both groups

Trials with clozapine (N = 1127); in both groups also favoured the combination therapy (RR 0.66 CI 53 to 0.83), but had high heterogeneity (I^2 = 64%) and no obviously outlying trials.

1.1.2 other atypical in both groups

Seven trials tested atypical in both groups (N = 674). There was not a clear difference between antipsychotic combinations and antipsychotic monotherapy within this subgroup (RR 0.95 CI 0.83 to 1.09).

1.1.3 typical drugs in both groups

We found five trials to be relevant to this subgroup, which included a total of 597 participants. For this outcome, we did find evidence that antipsychotic combinations reduced the risk of no response when compared with antipsychotic monotherapy (RR 0.64 CI 0.49 to 0.84). For this subgroup heterogeneity is moderately high (I^2 = 47%) but when the outlying trial C +perphenazine 1976 is removed the results show no heterogeneity.

1.2 Clinical response: 2. Relapse

Three trials (N = 512), with follow-up durations of eight weeks, one year and three years, respectively provided data regarding relapse. Results showed high heterogeneity (I^2 = 81%), when the outlying study (A +pimozide 1985) is removed heterogeneity is restored. But as this trial carries more than 10% of the weighting for this outcome, the results were not pooled. A +sulpiride 1994 and C +perphenazine 1976 found no difference between the two interventions. A +pimozide 1985 found that antipsychotics combinations is more effective for preventing relapse when compared to monotherapy.

1.3 Leaving the study early

Forty-three trials (N = 3137), with six weeks to one year follow-up found no difference in the number of people leaving the study early (RR 0.90 CI 0.76 to 1.07; Analysis 1.3, *low-quality evidence*). Subgroup analysis showed no important difference between groups.

1.4 Service utilisation: Hospital admission

Three trials (N = 202), with follow-up duration of eight, ten weeks and six months, respectively, provided data on hospital admission. Two trials tested clozapine in both groups, and the other tested any antipsychotics in both groups. A combination of antipsychotics was not superior or inferior to antipsychotic monotherapy in preventing hospital admission (RR 0.96 CI 0.36 to 2.55; Analysis 1.4, *very low-quality evidence*). None of the subgroups showed different results.

1.5 Clinical response: 3. Global state - i. average severity score (CGI-S scale, high = bad)

For this outcome we found seven relevant studies which provided endpoint data regarding global state on the severity component of the CGI scale, with six weeks to three years follow-up involving 496 participants. For this outcome, we did not find evidence that antipsychotic combinations was different in its effects compared with antipsychotic monotherapy (MD -0.13 CI -0.31 to 0.06, Analysis

1.5). This outcome had moderate levels of heterogeneity (I^2 = 44%). None of the subgroups showed different results.

1.6 Clinical response: 3. Global state - ii. change in severity score (CGI-S scale, high = bad)

Three relevant (N = 233) studies involving 233 participants only provided change data regarding this scale. For this outcome, we did not find evidence that antipsychotic combinations was clearly different in its effects compared with antipsychotic monotherapy (MD 0.11 CI -0.09 to 0.32; Analysis 1.6).

1.7 Clinical response: 4. Global state - average improvement score (CGI-I scale, high = bad)

Four trials, with ten to 16 weeks follow-up, measured global state on the improvement component of the CGI scale. We found that the combination therapy may improve clinical response when compared to monotherapy (MD -0.36 CI -0.58 to -0.13; Analysis 1.7).

1.8 Clinical response: 5. Global state - i. average functioning score (GAF scale, high = good)

We identified three studies relevant to this outcome, with 6 to 12 weeks follow-up, involving 107 participants. For this outcome heterogeneity is high (I^2 = 80%). When C +risperidone 2005 is removed, heterogeneity is restored but as this trial carries more than 10% of the weighting for this outcome, the results were not pooled and we only presented the data for the subgroups:

1.8.1 Clozapine in both groups

There is a single trial in this subgroup, which included a total of 30 participants. We found evidence that antipsychotics combination is worse than monotherapy for improvement of the global state (MD -4.5 CI -8.38 to -0.62; Analysis 1.8).

1.8.2 Other atypical drugs in both groups

There are two relevant trials in this subgroup, which included a total of 77 participants. We found evidence that the use antipsychotic combinations when compared to antipsychotic monotherapy improves the global state when assessed with the GAF scale (MD 8.73 CI 1.56 to 15.9; Analysis 1.8).

1.9 Clinical response: 5. Global state - ii. change in functioning score (GAF scale, high = good)

We found three studies (N = 349) which provided only change data for the GAF scale, we did not find evidence of a clear difference between the two treatments in this comparison (MD 0.27 CI -1.42 to 1.97; Analysis 1.9).

1.10 Mental state: 1. Overall - a.i average total score (PANSS scale, high = bad)

We identified 11 studies relevant to this outcome involving 721 participants. We did not find evidence of a clear difference between the two treatments in this comparison. This outcome had important levels of heterogeneity (I^2 = 58%). When B +ziprasidone 2014 and C +risperidone 2001 are removed, heterogeneity is decreased but as these trials carry more than 10% of the weighting for this outcome, the results were not pooled.

1.11 Mental state: 1. Overall - a.ii change in total score (PANSS scale, high = bad)

Eight studies (N = 406) only provided change data for the PANSS scale, we did not find evidence of a clear difference between the two treatments in this comparison (MD -1.05 CI -3.42 to 1.32; Analysis 1.11). Subgroup analysis showed no difference.

1.12 Mental state: 1. Overall - b.i. average total score (BPRS scale, high = bad)

We found 21 trials (N = 1082), with six weeks to six months follow-up, who reported data for mental state on the BPRS scale, but results showed high heterogeneity (I^2 = 92%; Analysis 1.12). Removal of the outlying studies C +sulpiride 1999b and C +sulpiride 2003 reduces heterogeneity for the clozapine subgroup (I^2 = 47%), but not for the pooled results (I^2 = 81%). Data were, therefore, not pooled for this outcome.

1.13 Mental state: 1. Overall - b.ii change total score (BPRS scale, high = bad)

We identified one study which only provided change data for this outcome involving 100 participants. We did find evidence that antipsychotic combinations improved the overall mental state when evaluated with the BPRS scale (MD -2.72 CI -5.37 to -0.07; Analysis 1.13).

1.14 Mental state: 2. Specific - a. positive symptoms - no clinical improvement

Two trials, with six and 10 weeks follow-up, reported binary data for no clinical improvement on positive symptoms, but the results showed high heterogeneity (I^2 = 80; Analysis 1.14). Data were, therefore, not pooled for this outcome. None of the studies showed a difference between the two groups.

1.15 Mental state: 2. Specific - b. positive symptoms - i. average score (PANSS scale, high = bad)

For this outcome we found four relevant studies involving 158 participants. We found evidence that participants assigned to antipsychotics combinations had a poorer response to the positive symptoms than patients assigned to antipsychotics monotherapy (MD 2.02 CI 0.90 to 3.14; Analysis 1.15). The results are due to the trials in the subgroup where clozapine was used in both groups.

1.16 Mental state: 2. Specific - b. positive symptoms - ii. change score (PANSS scale, high = bad)

We identified nine studies who reported only change data for the positive symptoms assessed with the PANSS scale. We did not find evidence of a clear difference between antipsychotic combinations and antipsychotic monotherapy (MD 0.01 CI -0.45 to 0.47; Analysis 1.16).

1.17 Mental state: 2. Specific - b. positive symptoms - iii. average score (BPRS scale, high = bad)

We identified three studies, with a follow-up time between eight and 16 weeks, we did not find evidence of a clear difference between antipsychotic combinations and antipsychotic monotherapy (MD -1.02 CI -2.42 to 0.38; Analysis 1.17). This outcome had moderate levels of heterogeneity (I^2 = 41%). We did not find a difference in the results between subgroups.

1.18 Mental state: 2. Specific - b. positive symptoms - iv. change data (BPRS scale, high = bad)

We identified one study (N = 17) which only reported change data for the positive symptoms when assessed with the BPRS scale. We did not find evidence of a clear difference between antipsychotic combinations and antipsychotic monotherapy (MD -0.3 CI -1.16 to 0.56; Analysis 1.18)

1.19 Mental state: 2. Specific - b. positive symptoms - v. average score (SAPS scale, high = bad)

We identified one study relevant to this outcome involving 28 participants. For this outcome, we did find evidence that antipsychotic combinations is better than monotherapy for the positive symptoms when assessed with the SAPS scale (MD -6.76 CI -11.91 to -1.61, Analysis 1.19).

1.20 Mental state: 2. Specific - b. positive symptoms - vi. change score (SAPS scale, high = bad)

One study provided only change data for this scale. We found evidence that antipsychotic combinations is better at reducing the positive symptoms when compared to monotherapy (MD -5.8 CI -11.33 to -0.27, Analysis 1.20).

1.21 Mental state: 3. Specific - a. negative symptoms - no clinical improvement

Three trials, with six to ten weeks follow-up, reported binary data for no clinical improvement on negative symptoms, but the results showed high heterogeneity (I^2 = 65; Analysis 1.21). Removal of C +risperidone 2005 restores homogeneity and the results become significant (RR 0.80 CI 0.65 to 0.98), but as this trial carries more than 10% of the weighting for this outcome, the results were not pooled.

1.22 Mental state: 3. Specific - b. negative symptoms - i. average score (PANSS scale, high = bad)

For this outcome we found five relevant studies involving 194 participants. For this outcome heterogeneity is high (I^2 = 57%). The heterogeneity is due to B +any antipsychotic 2013 which belongs to the subgroup 'Any antipsychotic in both groups', when this trial is removed heterogeneity is resolved. Because this trial carries more than 10% of the weighting for this outcome, the results were only presented in subgroups.

1.22.1 clozapine in both groups

We found three trials to be relevant to this subgroup (N = 119). For this subgroup, we did not find evidence of a clear difference between the two treatments (MD 0.31 CI -1.18 to 1.8; Analysis 1.22).

1.22.2 other atypical drugs in both groups

We found one trial to be relevant to this subgroup, with a total of 36 people. For this subgroup, we did not find evidence of a clear difference between the two treatments (MD 1.2 CI -1.51 to 3.91; Analysis 1.22).

1.22.3 Any antipsychotic in both groups

We found one trial to be relevant to this subgroup, with a total of 39 people. We found evidence that antipsychotics combinations is worse for improving the negative symptoms when compared to antipsychotic monotherapy (MD 3.3 CI 1.6 to 5.0; Analysis 1.22).

1.23 Mental state: 3. Specific - b. negative symptoms - ii. change score (PANSS scale, high = bad)

We identified nine studies involving 891 participants. The studies only reported change score. We did not find evidence of a clear difference between antipsychotic combinations and antipsychotic monotherapy (MD 0.02 CI -0.54 to 0.58, Analysis 1.23). No important difference was found between subgroups.

1.24 Mental state: 3. Specific - b. negative symptoms - iii. average score (BPRS scale, high = bad)

We identified two studies relevant to this outcome. We did not pooled the data because heterogeneity was high (I^2 = 56%) and we only present the results by subgroups.

1.24.1 clozapine in both groups

There is a single trial in this subgroup, which included a total of 61 participants. There was not a clear difference between antipsychotic combinations and antipsychotic monotherapy within this subgroup (MD -4.3 CI -12.25 to 3.65; Analysis 1.24).

1.24.2 other atypical drugs in both groups

There is a single trial in this subgroup, which included a total of 40 participants. We found evidence that antipsychotic combinations is worse at improving the negative symptoms when compared to antipsychotic monotherapy (MD 1.9 CI 0.69 to 3.11; Analysis 1.24)

1.25 Mental state: 3. Specific - b. negative symptoms - iv. change score (BPRS scale, high = bad)

For this outcome we found a single trial (N = 12). We did not find evidence of a clear difference between antipsychotic combinations and antipsychotic monotherapy (MD 0.2 CI -0.29 to 0.69; Analysis 1.25)

1.26 Mental state: 3. Specific - b. negative symptoms - v. average score (SANS scale, high = bad)

Eleven trials, with six to 16 weeks follow-up, measured negative symptoms on the SANS scale (Analysis 1.26). These results were not pooled in the analysis as they showed high heterogeneity (I^2 = 96%). Most studies tested clozapine in both groups, but again with high heterogeneity (I^2 = 93%). Removing the outlying trials C +risperidone 2005b, B +sulpiride 1996, C +sulpiride 1999b and C +sulpiride 2003 does restore heterogeneity for the clozapine subgroup but does not affect the overall results. They account for more than 10% of the weighting and so again, results are not pooled. No important difference was found for other atypical drugs or typical in both groups.

1.27 Mental state: 3. Specific - b. negative symptoms - vi. average score (SANS scale, high = bad)

We found one trial who only reported change data for this scale, which included a total of 28 participants. We found evidence that the use of antipsychotic combinations is better at improving the negative symptoms when compared to antipsychotic monotherapy (MD -6.80 CI -12.65 to -0.95; Analysis 1.27).

1.28 Mental state: 4. Specific - aggression/agitation - average score (BPRS scale, high = bad)

One trial (N = 12), with a follow-up duration of eight weeks, only provided data for change in aggression/agitation symptoms when

assessed with the BPRS scale. We found evidence in favour of combination therapy in improving aggression/agitation symptoms (MD -1.30 CI -2.32 to -0.28; Analysis 1.28).

1.29 Adverse events: 1. General - a. serious event or requiring discontinuation

Thirty trials (N = 2398), with six weeks to eight months follow-up, did not find an important difference in the number of adverse events that were serious or required discontinuation (RR 1.05 CI 0.65 to 1.69; Analysis 1.29, *very low quality of evidence*). None of the subgroups of antipsychotics showed a significant difference.

1.30 Adverse events: 1. General - b. death (suicide or non-suicide deaths)

Only four trials reported on deaths, with follow-up durations of eight to 12 weeks. There was only one death reported in the combination group and no deaths in the monotherapy group Analysis 1.30.

1.31 Adverse events: 2. Movement disorders - a. any

Twenty trials, with 30 days to three years follow-up, provided binary data regarding movement disorders. No difference was found between combination therapy and monotherapy in the number of participants experiencing movement disorders (RR 1.07 CI 0.92 to 1.25; N = 1868; studies = 20; Analysis 1.31), and none of the subgroups of antipsychotics showed a significant difference.

Movement disorders were also measured on eight scales (Barnes Akathisia Scale (BAS), Abnormal Involuntary Movement Scale (AIMS), Simpson Angus Scale (SAS), Udvalg for Kliniske Undersøgelser (UKU), Treatment Emergent Symptom Scale (TESS), Extrapyramidal SymptomRating Scale (ESRS) and Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS). However, much of the data were considerably skewed and are reported in Appendix 7.

1.32 Adverse events: 2. Movement disorders - b.i. average scores (SAS, high = bad)

Nine trials reported on movement disorders using the SAS, but in six of them, the data were very skewed and not added to the analysis. The pooled data for the three remaining trials showed very high heterogeneity (I^2 = 99%; Analysis 1.32) and so were not pooled. The heterogeneity might be due to the difference in the properties of the drugs, as C +fluphen dec 2009 is using a typical antipsychotic.

1.33 Adverse events: 2. Movement disorders - b.ii. change scores (SAS, high = bad)

We found one trial (N = 63) who only reported change data for the SAS scale, which also did not showed any difference between the two intervention groups (Analysis 1.33).

1.34 Adverse events: 2. Movement disorders - b.iii. average scores (TESS, high = bad)

Again, three out of the five trials that reported movement disorders on the TESS reported skewed data. Heterogeneity was very high for the other two trials (I^2 = 99%) and so they were not pooled. Similarly to the findings on the SAS, the trial (C +CPZ 1999) using a typical antipsychotic resulted in worse movement disorders for the combination group (MD 5.80 CI 5.03 to 6.57; Analysis 1.34); the trial with other atypical drugs showed no difference between monotherapy and combination.

1.35 Adverse events: 2. Movement disorders - b.iv. average scores (DIEPSS, high = bad)

One trial (C +aripiprazole 2008), with a follow-up duration of eight weeks, which tested clozapine in both the combination and monotherapy groups, found no important difference in movement disorders when measured on the DIEPSS scale (MD 0.30 CI -0.49 to 1.09; participants = 61; studies = 1; Analysis 1.35).

1.36 Adverse events: 2. Movement disorders - b.v. change scores (BAS, high = bad)

Ten trials reported on movement disorders using the BAS, but in eight, data were very skewed and were not added to the analysis. Two trials, with follow-up duration of six weeks, which tested atypical antipsychotics in both the combination and monotherapy groups, found no significant difference in movement disorders when measured on the BAS scale (MD -0.70 CI -1.54 to 0.14; N = 91; studies = 2; Analysis 1.36). C +aripiprazole 2015b reported that all participants scored zero at follow-up.

1.37 Adverse events: 2. Movement disorders - b.vi. change scores (AIMS, high = bad)

Five trials reported on movement disorders using the AIMS, but in four studies data were very skewed and not added to the analysis. One trial (N = 63), with follow-up duration of six weeks, which tested atypical antipsychotics in both the combination and monotherapy groups, found no significant difference in movement disorders when measured on the AIMS scale (MD 0.10 CI -0.84 to 1.04; Analysis 1.37).

1.38 Adverse events: 3. Endocrine - prolactin level (high = bad)

Fifteen trials reported prolactin levels, but in eight, data were very skewed and not added to the analysis. In the seven remaining trials with six to 16 weeks follow-up, the pooled data regarding change in prolactin level had very high heterogeneity (I^2 = 98%, Analysis 1.38). For studies with clozapine in both groups, data were also highly heterogeneous (I^2 = 98%). When we split the data by trials using aripiprazole as the add-on antipsychotic, the heterogeneity is reduced (I^2 = 66%) for the trials not using aripiprazole as an intervention. Data were not pooled for this outcome.

1.39 Adverse events: 4. Metabolic - a. weight gain (binary)

Six trials (N = 804), with six to 16 weeks follow-up, provided data regarding the number of participants experiencing weight gain. No significant difference was found in the number of participants experiencing weight gain (RR 1.00 CI 0.66 to 1.53; Analysis 1.39).

1.40 Adverse events: 4. Metabolic - b. average weight gain (kg)

Nine trials, with six to 16 weeks follow-up, provided data regarding average weight gain, but results showed high heterogeneity (I^2 = 53%; Analysis 1.40). When B +aripiprazole 2008 is removed from the analysis, the heterogeneity is reduced (I^2 = 4%), but as this trial carries more than 10% of the weighting for this outcome, the results were not pooled.

1.41 Adverse events: 5. Blood - a. decreased white cell counts (binary)

Two trials (N = 315), tested clozapine in both groups with eight to 12 weeks follow-up provided data regarding number of participants experiencing decreased white cell counts. A significant difference

was found in favour of the combination therapy (RR 0.18 CI 0.04 to 0.82; Analysis 1.41). The result could be explained by a dose-dependant side effect. The studies used higher doses in the clozapine monotherapy group when compared with the doses used in the combination group.

1.42 Adverse events: 5. Blood - b. average white cell counts (10-3/mm3)

One trial (N = 61) with eight weeks follow-up reported data for white blood cell counts. No significant difference was found between the monotherapy and combination groups (MD 0.66 CI - 0.20 to 1.52; Analysis 1.42). A further four trials measured white blood counts but did not report any data: C +aripiprazole 2008 also found no difference between groups, C +risperidone 2005b and C +sulpiride 1997 reported that there were no changes in white blood cell counts.

1.43 Adverse events: 6. Central nervous system (CNS) - a. drowsiness

Eleven trials, with six to 16 weeks follow-up, provided data regarding drowsiness, but results showed high heterogeneity (I^2 = 67%; Analysis 1.43). When the outlying trials C +risperidone 2001 and C +sertindole 2006 are removed from the analysis heterogeneity restores both for the clozapine group and overall. As these trials carry more than 10% of the weighting for this outcome, the results were not pooled.

1.44 Adverse events: 6. Central nervous system (CNS) - b. tremor

Four trials (N = 22), with six to 12 weeks follow-up, found no significant difference in the number of patients in the monotherapy or combination therapy groups experiencing tremors (RR 0.87 CI 0.47 to 1.62; Analysis 1.44)

1.45 Quality of life: 1a. Average score (QLS high=good)

C +risperidone 2005 with 30 participants and a follow-up of six weeks, tested clozapine in both groups. This trial measured quality of life on the QLS scale and found no important difference between treatment groups (MD 0.80 CI -5.44 to 7.04; Analysis 1.45).

1.46 Quality of life: 1b. Average score (SWN, high=good)

Two trials with eight to 16 weeks follow-up, which tested clozapine in both groups measured quality of life on the SWN scale and found no significant difference between treatment groups (MD 2.05 CI -1.08 to 5.18; Analysis 1.46). B +quet/risp 2009 also used the SWN scale, but did not report SDs and no suitable means were available to impute the data.

1.47 Quality of Life: 1c. Average score - Mental component summary (SF-36, high = good)

C +sulpiride 2013 (N = 60) with a follow-up of six weeks, measured the mental component of quality of life on the SF-36 scale and found no significant difference between treatment groups (MD 0.60 CI -4.28 to 5.48; Analysis 1.47).

1.48 Quality of Life: 1d. Average score - Physical component summary (SF-36, high = good)

Again, C +sulpiride 2013 (N = 60) with a follow-up of six weeks, measured the physical component of quality of life on the SF-36 scale and found no significant difference between treatment groups (MD -1.70 CI -4.71 to 1.31).

2. Other outcomes

Although A +reserpine 1957, B +any antipsychotic 2013, C +CPZ 1973 and C +pimozide 2011 measured behaviour and social functioning (on four different scales), none reported data that could be used in the analysis. Data were also not available on number of days in hospital, change in hospital status, employment status during trial, occurrence of violent incidents, levels of substance abuse, adverse events requiring hospitalisation, and allergic reactions. Studies did not report economic burden (cost of care), although two trials reported the cost of the therapies; C +haloperidol 2010 reported the cost of the combination therapy (2mg per day risperidone plus 2 mg per day haloperidol, $1.26 per day) was approximately half the cost of the monotherapy (4 mg per day risperidone, $2.40) and C +sulpiride 2013 reported the cost of the combination therapy (amisulpride 400 mg per/day plus sulpiride 800 mg/day, US$2.82/day) was also approximately half of the cost of monotherapy (amisulpride 800 mg/day, $4.88/day).

3. Subgroup analyses for clinical response: not clinically improved

We used random-effects model for subgroup analyses. No subgroup differences were found for clinical response for subgroup analyses of chronic versus acutely ill people, length of treatment less than 12 weeks versus more than 12 weeks and between studies that tested clozapine in both groups versus all other studies (Analysis 1.49; Analysis 1.50; Analysis 1.51). A subgroup difference was found between the drugs added to clozapine (P = 0.009; Analysis 1.52) with pipotiazine and sulpiride favouring the combination of antipsychotics and risperidone showing no differences in the number of participants not clinically improved. The pooled results showed high heterogeneity (I^2 = 64%). However, when the risperidone subgroup is removed heterogeneity is restored.

In the meta-regression, we did not found an effect or an interaction by the potential modifiers: year of publication and Chinesse origin. The meta-regression model adjust was poor (0.00%) (Table 1).

4. Subgroup analyses for leaving the study early

No subgroup differences were found for leaving the study early for the subgroup analyses of chronic versus acutely ill people, length of treatment less than 12 weeks versus more than 12 weeks, between studies that tested clozapine in both groups versus all other studies and between the drugs added to clozapine (Analysis 1.53; Analysis 1.54; Analysis 1.55; Analysis 1.56).

5. Sensitivity analyses for clinical response: not clinically improved

Three studies (B +sulpiride 1996; C +sulpiride 1999; C +sulpiride 1999b) which reported data for clinical response had a high risk of bias for sequence generation. A significant subgroup difference (P = 0.03; Analysis 1.57) was found between studies with a low or unclear risk of bias versus those with a high risk of bias for randomisation, with both groups favouring the combination of antipsychotics. No subgroup difference was found between studies with a low or unclear risk of bias versus those with a high risk of bias for blinding (Analysis 1.57). When data are synthesised using

a fixed-effect model, results remain unchanged (RR 0.74 CI 0.68 to 0.81; Analysis 1.59).

6. Sensitivity analyses for leaving the study early

Only one study that reported data for leaving the study early had a high risk of bias for sequence generation (C +fluphen dec 2009). This small study reported no losses to follow-up and so no sensitivity analysis was possible (Analysis 1.60). No subgroup difference was found between studies with a low or unclear risk of bias versus those with a high risk of bias for blinding (Analysis 1.61). When data for is synthesised using a fixed-effect model the results remain unchanged (RR 0.87, 95% CI 0.76 to 1.00, Analysis 1.62) except for studies that tested typical drugs in both groups and any antipsychotic in both groups in which the combination therapy was favoured.

DISCUSSION

Summary of main results

The summary below reflects the outcomes chosen for the 'Summary of findings' table, and considers the main findings of this review that can support evidence-based decision making. For all outcomes included in the 'Summary of findings' table the quality of evidence was found to be either low or very low. Overall, findings from this review are that combination therapy does not have clear differences in its effects compared with monotherapy.

1. Clinical response: not clinically improved

Overall, we found evidence that combination therapy may be superior to monotherapy in improving clinical response. Subgroup analyses of different combinations of antipsychotics showed that this effect was due to the trials who included either clozapine in both groups or atypical drugs in both groups. It is important to note that these findings are mostly from short-term trials (22 trials of 12 weeks or less). Only two long-term trials (one year and three years) were identified. We, therefore, do not know what the efficacy might be if more trials had measured this outcome in the long term. Also, the definition of clinical response varied considerably across the studies hindering the interpretation of the findings. The finding that typical drugs in both groups may improve clinical response should be taken with caution, as all of the studies were undertaken more than 30 years ago, and translating these data to the actual clinical setting may be problematic. Nonetheless, the finding that adjunctive antipsychotic drug to either clozapine or a typical antipsychotics remains an interesting finding and worth considering to be the focus of further work. The very low quality of the evidence, as assessed with GRADE, diminish the confidence that can be placed in the magnitude of the effect.

2. Clinical response: relapse

There was a lack of information within the studies regarding relapse, most likely due to the duration of the trials (see above), and failure to report this outcome in the trials that were longer. Only three studies reported relapse - two of which were older studies comparing typical antipsychotics in both groups (A +pimozide 1985; C +perphenazine 1976) and one, a more recent trial, testing clozapine in both groups (A +sulpiride 1994). There was a lot of heterogeneity for this outcome, perhaps unsurprisingly given such different treatment drugs and lengths of trials: A +pimozide 1985 showed an important efficacy in favour of the combination treatment group for typical drugs over one year, and C +perphenazine 1976 showed no difference over the course of eight weeks. A +sulpiride 1994, however, showed no difference over three years for clozapine in both groups. Currently, there is only sparse evidence on relapse for typical antipsychotic combination therapy and clozapine combination therapy, and oddly, a complete lack of evidence regarding other atypical drugs in combination.

3. Leaving the study early

In 43 RCTs between 0% and 74% (average ~ 16%) of people receiving antipsychotics (combination or monotherapy) left the study early. Overall, there was not convincing evidence that, at least within trials, combined antipsychotic treatment was any different to monotherapy for helping people stay longer. People do leave early for a variety of reasons, but the combination therapies did not clearly prevent or encourage this. A common precursor to relapse is stopping medication. Combining antipsychotics does not seem to prevent or encourage cessation, although generalising from these studies to the real world is problematic. Nine studies - four with clozapine in both groups (C +risperidone 2005b; C +risperidone 2001b; C +sulpiride 1997; C +sulpiride 1999c), four with other atypical drugs in both groups (C +arip/pali 2014; C +clozapine 2001; C +clozapine 2013; C +fluphen dec 2009), and one with typical drugs in both groups (A +trifluoperazine 1964) - had no participants leave early at all and were therefore not accounted for in the general analysis.

4. Hospital admission

There was a lack of studies contributing to this outcome, most likely attributed to the setting of the trials as most were performed in an inpatient setting. Of the three included trials only one was long term (A +any antipsychotic 2011) and contributed to 80.7% of the weight for this outcome. No difference was found between treatment groups in the number of participants hospitalised.

5. Adverse events

We did not find evidence of a difference between treatment groups in serious adverse events or those requiring discontinuation; neither subgroup analysis showed a significant difference. There were no reports of agranulocytosis. Although there were no differences in serious adverse events in the short term, we are not able to say whether there is a difference in serious adverse events when using these therapies in the long term as most of the data is from short-term trials (22 trials of 12 weeks or less). Nine studies had no serious adverse events or an event requiring discontinuation at all and were therefore not accounted for in this general analysis. There was no evidence of a difference in the number of patients experiencing movement disorders or weight gain.

5. Quality of life

There is a lack of evidence on quality of life, with only four studies reporting data for this outcome on three different scales, none of which showed a difference between treatment groups.

Overall completeness and applicability of evidence

1. Completeness

We did not find any trials with data for the following outcomes: days in hospital, change in hospital status, general behaviour, specific behaviours, social functioning, employment status during the trial,

occurrence of violent incidents, and level of substance abuse. Quality of life, independence and the ability to work are important outcomes for those living with schizophrenia. Very few studies reported data for these outcomes and, those that did, reported data that are not really clinically meaningful.

We are aware of one study (NCT01450514) that looked at the effects of a combination therapy versus monotherapy. We tried to obtain data from this trial but the sponsor decided not to provide data as they wanted to keep it confidential.

For studies that had both clozapine and another antipsychotic in two monotherapy groups, we only included the data from the clozapine arm, as we considered this to be the more important comparison and in order to facilitate subgroup analyses.

This review compares only monotherapy with combination therapy, and we do not make direct comparisons between different types of combinations of antipsychotics, e.g. combinations including typical antipsychotics versus those containing clozapine.

2. Applicability

The majority of studies were less than 12 weeks in duration, with 10 trials longer or equal to six months and, as schizophrenia is a chronic disease with a long-term course, there is only limited information about the long-term safety and efficacy of antipsychotic combination therapy. Most trials were undertaken in very formalised settings - not at all reflective of the everyday circumstances in which people with schizophrenia live. This must also reduce applicability. Long trials set in very real-world circumstances are needed.

Quality of the evidence

As can be seen graphically in Figure 1 we felt the risk of bias in the included studies to be moderate to high. The majority of trials had unclear allocation concealment, method of randomisation and blinding, and were not free of selective reporting. Only around half of the studies addressed incomplete data adequately and in most it was unclear if they were free from other biases. There is a real danger in unfairly judging studies of the past by today's standards. However, this may not be as unfair as it seems. For mental health there is some evidence that reporting of trials was as good if not better in the 1960s and 1970s than it was two decades later (Ahmed 1998). However, the CONSORT initiative was formalised in 1996 (Begg 1996), and only eight of the 62 included trials predated this. That only 18 trials reported adequate generation and 16 the methods used to conceal allocation reflects poor quality reporting, probably poor [biased] conduct, and is certainly associated with exaggerated estimates of effect (Schulz 1995).

The sensitivity analysis for the quality of reporting of randomisation did not suggest that the less convincingly randomised studies produced discernibly different results, nor did the sensitivity analysis for the blinding of studies.

Potential biases in the review process

In our search strategy we tried to identify all relevant trials. However, there is the possibility that we may have failed to identify some studies. We have worked only with published reports. By doing this we may be perpetuating a reporting and publishing bias. It would be better to have original individual patient data.

The extraction of data and the risk of bias for the Chinese language studies were completed by only one review author. There is the possibility that this may have introduced some bias into the results as it was not possible to cross-check these data.

Agreements and disagreements with other studies or reviews

We know of seven other reviews that compare various combinations of antipsychotics. Correll 2009 addressed the same topic as the current review and reported that antipsychotic combination therapy was superior to monotherapy for inefficacy and leaving the study. In our analysis we also found an effect in favour of the combination therapy for inefficacy, but did not find a clear difference between treatments for leaving the study early. This difference in findings was due to our inclusion of more data from recently published studies. For example, for the outcome of 'leaving the study early', in Correll 2009 the weighting for data from the trial A +pimozide 1985 was 90%. For our review the weighting for these data from A +pimozide 1985 was only 12.6%. This illustrates how fast evidence can change with emergence of new data and the need for regular updating of review.

The relevant Canadian Agency for Drugs and Technologies in Health overview (CADTH 2012) presented results in subgroups for clozapine in both groups and other atypical drugs in both groups. Our findings were the same for efficacy, serious adverse events and leaving the study early.

A further five reviews looked specifically at the augmentation of clozapine with another antipsychotic. Barber 2017 included participants with treatment-resistant schizophrenia and found efficacy in favour of the clozapine combination in open-label studies but not double-blind studies. This contrasts with our results, as in this review trials with a low or an unclear risk of bias for blinding favoured the combination of antipsychotics. Sommer 2012 reviewed pharmacological augmentation of clozapine. Our results did not differ from this review in regards to aripiprazole, haloperidol, risperidone and sulpiride augmentation. C +aripiprazole 2009 reviewed sulpiride augmentation of clozapine and includes the same studies as our review, and the findings are the same. Taylor 2009 also found efficacy in favour of combination therapy; however, they dealt with data differently from our review by combining data from the Brief Psychiatric Rating Scale (BPRS) and Positive and Negative Syndrome Scale (PANSS), so it is not possible to compare the findings. They found no difference in leaving the study early, which is the same as our findings. Meng 2015 reviewed pharmacological augmentation with aripiprazole for participants with antipsychotic-induced hyperprolactinaemia. They reported data differently from our review as they presented a dichotomous outcome for the proportion of participants whose prolactin levels returned to normal; their results favoured the use of aripiprazole. They also found no difference in leaving the study early.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with schizophrenia

Currently, there is very low-quality evidence that the use of antipsychotic combinations results in a clinical improvement when compared with monotherapy. There is no evidence that

combination antipsychotic therapy does that much, either in terms of leaving the study early and/or adverse events. Quality of evidence is low and unique positive reactions to combinations of drugs do occur. All we can say is that combinations do not have a clear advantage over monotherapy from within the context of trials.

2. For clinicians

As a clinician it is common to find a person on a combination of antipsychotics or to be tempted to add other drugs to an already established, but clearly inadequate antipsychotic regimen. This review does not preclude adding an additional antipsychotic, nor does this review suggest that discontinuation of one of the two combination antipsychotics is necessarily indicated. All should be done with caution due to lack of sufficient evidence. It would be beneficial if clinicians that face the clinical question addressed in this review, began to randomise their patients to contribute to the body of evidence.

3. For policymakers

It would seem sensible that the fewer antipsychotics, the better - but some people do seem to do well on combinations of antipsychotics and there is a risk of upsetting this group of people by stipulating that it is going against policy to have people on more than one antipsychotic. Furthermore, there is not good quality evidence for this stipulation.

Implications for research

1. General

Registration of trials before anyone is randomised would ensure that participants could be confident that people would know that the study had at least taken place. Unique study numbers would help researchers identify single studies from multiple publications and reduce the risk of duplicating the reporting of data.

Compliance with CONSORT would help clarify methodology and many outcomes. Failure to do this results in both loss of data and confusion in the results.

2. Specific

2.1 Trials

It would be beneficial to people with schizophrenia if there was a long-term (e.g. > one year) trial comparing antipsychotics combination with monotherapy. The outcomes measured should include leaving the study early, clinical improvement, relapse, adverse events and quality of life, which is an important outcome that has been overlooked in most trials. We do realise that such a study is a considerable undertaking and that we have only reviewed others' work in this area. However, that does give a perspective and we have suggested a design of study in Table 2.The fact that the last clinical trials which used a combination of typical antipsychotics was more than 30 years ago, is concerning as this review suggests the use of these drugs might have a place in the care of the patients with schizophrenia. Overlooking the typical antipsychotics in the design of new trials could potentially mislead the consumers to use more atypical antipsychotics.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

A +any antipsychotic 2011

Methods	**Allocation:** randomised.

A +any antipsychotic 2011 *(Continued)*

	Blinding: open-label. **Duration:** 6 months. **Setting:** outpatients. **Design:** parallel. **Country:** USA, multi-centre.
Participants	**Diagnosis:** schizophrenia or schizoaffective disorder (DSM-IV). **N** = 127. **Sex:** M 84, F 43. **Age:** > 18 years. **History:** patients taking any two prescribed antipsychotic medications with persistent psychopathology or significant side effects and no exacerbation within the past 3 months.
Interventions	1. **Combination therapy:** stay on antipsychotic combination (any combination of anti-psychotic medication)* (N = 62). 2. **Monotherapy:** switch to antipsychotic monotherapy within 30 days** (N = 65). **Schedule:** no details of doses.
Outcomes	**- Usable data -** 1. Leaving the study early. 2. Service utilisation: hospital admission. 3. Adverse events: serious event or requiring discontinuation, movement disorders. **- Unable to use -** 1. Change in prolactin level (not reported). 2. Adverse events: AIMS, SAS (not reported). 3. Adverse events: weight gain (not reported). 4. Adverse events: blood levels (not reported). **- Not used in review -** 1. Time to all-cause treatment discontinuation, ASEX physiological measurements, BMI.
Notes	*The most common antipsychotic combinations were quetiapine and risperidone, quetiapine and a first-generation antipsychotic, risperidone and a first-generation antipsychotic, olanzapine and a first-generation antipsychotic, ziprasidone and a first-generation antipsychotic, aripiprazole and quetiapine and olanzapine and risperidone. **12 (21%) discontinued quetiapine, 10 (17%) discontinued risperidone, nine (15%) discontinued olanzapine, eight (14%) discontinued haloperidol, and the remaining 19 (33%) discontinued other antipsychotics (each at less than 10% of discontinuations).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The study's project director used a single predetermined randomisation stream (i.e., without stratification)", no further details provided.
Allocation concealment (selection bias)	Low risk	Central allocation, "to maintain blinding, randomisation was managed centrally".
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label, participants and personnel were not blinded, Assessment by blinded clinical raters, precautions were taken not to reveal treatment allocation to raters.

A +any antipsychotic 2011 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT method was used for primary analyses. 14% discontinued from the combination group and 31% from the monotherapy group, reasons for discontinuation were provided.
Selective reporting (reporting bias)	High risk	Not all pre-stated outcomes were fully reported.
Other bias	Low risk	Supported by NIMH.

A +any antipsychotic 2012

Methods	**Allocation:** randomised. **Blinding:** open-label. **Duration:** 8 months. **Setting:** outpatient. **Design:** parallel. **Country:** not reported.
Participants	**Diagnosis:** schizophrenia or delusional disorder diagnosis (DSM-IV). **N** = 60. **Sex:** M 36, F 24. **Age:** Not specified. **History:** Taking 1 antipsychotic medication when they entered study.
Interventions	1. **Combination therapy:** switch to dual antipsychotics by adding up another medication* (N = 30). 2. **Monotherapy:** assigned to continue receiving monotherapy (N = 30).
Outcomes	**- Usable data -** 1. Leaving the study early. **- Unable to use -** 1. Clinical response: GAF (Not reported). 2. Mental state: BPRS (Not reported). **- Not used in this review -** 1. BMI and Lunsers scale.
Notes	* From report: “Choice of medication to add was left to prescribe and patient and also at their discretion the dose of all drug could be raised or lowered.”

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“randomly allocated.” No other information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias)	High risk	“Choice of medication to join was left to prescriber and patient and also at their discretion the dose of all drug could be raised or lowered

A +any antipsychotic 2012 *(Continued)*

All outcomes		." "Outcomes were performed by trained assessor masked to allocated treatment."
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout: 18 (30%) not equally subdivided between the two groups.
Selective reporting (reporting bias)	High risk	No mean and SD deviation reported for BPRS and GAF.
Other bias	Unclear risk	None obvious.

A +any antipsychotic 2015

Methods	**Allocation:** randomised. **Blinding:** open-label. **Duration:** 360 days. **Setting:** outpatient. **Design:** parallel. **Country:** USA, multi-centre.
Participants	**Diagnosis:** schizophrenia or schizoaffective (DSM IV-TR). **N** = 104. **Age:** ~ 45 years. **Sex:** male and female. **History:** chronic, stable patients, who had been receiving 2 antipsychotic medications concurrently for at least 90 days (average duration of antipsychotic polypharmacy was 2.5 years).
Interventions	1. **Combination therapy (Stay):** stay participants were required to remain on the two antipsychotic medications they were currently receiving (N = 52). 2. **Monotherapy (Switch):** required to switch from the two antipsychotics they were currently receiving to one of these two within 60 days of baseline assessments (N = 52).
Outcomes	**- Usable data -** 1. Leaving the study early. **- Not able to use -** 1. Clinical response: CGI-S, CGI-I (Unable to impute). 2. Mental state: PANSS (Unable to impute). 3. Adverse events: BAS, SAS, AIMS (Unable to impute). **- Not used in this review -** 1. BMI, lipids, HbA1C.
Notes	
Risk of bias	

A +any antipsychotic 2015 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The research coordinator at each site applied a site-specific random assignment protocol." Insufficient information about the sequence generation process.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement.
Blinding (performance bias and detection bias) All outcomes	High risk	"While treatment was open-label, baseline and subsequent assessments were conducted by "independent assessors" blinded to the research status of participants."
Incomplete outcome data (attrition bias) All outcomes	High risk	"21% discontinued from the combination group and 52% from the monotherapy group, reasons for discontinuation were not provided for all participants."
Selective reporting (reporting bias)	High risk	No usable data for CGI-S, CGI-I, PANSS, BAS, SAS and AIMS.
Other bias	High risk	"the switch and stay groups differed significantly on baseline antipsychotic dose with stay participants receiving an average of 8 mg more olanzapine equivalents per day" Baseline dose imbalances. This study was funded by the Florida Agency for Health Care Administration.

A +pimozide 1985

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 1 year. **Setting:** outpatients. **Design:** parallel. **Country:** Japan.
Participants	**Diagnosis:** remitted schizophrenics (DSM-III). **N** = 106. **Sex:** M 78, F 28. **Age:** ~ 39 years. **History:** recovery stage of remission or residual phase, had reported regularly to the hospital.
Interventions	1. **Combination therapy:** thioridazine 25 mg + pimozide 2 mg (N = 11). 2. **Combination therapy:** thioridazine 25 mg + pimozide 6 mg (N = 12). 3. **Combination therapy:** thioridazine 75 mg + pimozide 2 mg (N = 11). 4. **Combination therapy:** thioridazine 75 mg + pimozide 6 mg (N = 13). 5. **Monotherapy:** thioridazine 25 mg (N = 12). 6. **Monotherapy:** thioridazine 75 mg (N = 10). 7. **Monotherapy:** pimozide 2 mg (N = 13). 8. **Monotherapy:** pimozide 6 mg (N = 11). **Schedule:** Daily doses.
Outcomes	**- Usable data -** 1. Leaving the study early.

A +pimozide 1985 *(Continued)*

	2. Clinical response: not clinically improved. 3. Adverse events: relapse. **- Unable to use -** 1. Adverse events: prolactin levels (data not reported).
Notes	*Data from a previous study were used as a retrospective placebo group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Each patient was randomly assigned to one drug treatment in a double-blind design.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding (performance bias and detection bias) All outcomes	Low risk	Drug appearance, with respect to powder colour, taste, and volume, was made identical by adding a common gastric aid, SMP.
Incomplete outcome data (attrition bias) All outcomes	High risk	6 patients who took drugs irregularly were excluded from the final analysis. Other patients discontinued designated use of the assigned drugs either through overdosage (N = 21) or because of relapse (N = 55).
Selective reporting (reporting bias)	High risk	Not all expected outcomes reported.
Other bias	Unclear risk	Source of funding not reported.

A +reserpine 1957

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 6 months (2 months baseline, 3 months before cross-over to a second follow up of 1 month). **Setting:** inpatients. **Design:** cross-over. **Country:** USA.
Participants	**Diagnosis:** regressed schizophrenic patients (regression, withdrawal, and intellectual disorganisation). **N** = 32. **Sex:** not reported. **Age:** average ˜ 35 years. **History:** chronic, regressed schizophrenia, had received prolonged courses of ECT, insulin, and "total push" programs, without lasting benefit.
Interventions	1. **Combination therapy:** reserpine + chlorpromazine (N = 10). 2. **Monotherapy:** reserpine (N = 10). 3. **Monotherapy:** chlorpromazine (N = 10). **Schedule:** reserpine 1 mg to 4 mg/day + chlorpromazine 100 mg to 400 mg/day, reserpine 4 mg to 8 mg/day, chlorpromazine 200 mg to 1200 mg/day. The medications were given at noon and 8:00 each day.

A +reserpine 1957 *(Continued)*

Outcomes	**- Usable data -** 1. Leaving the study early. 2. Clinical response: not clinically improved. 3. Adverse events: serious or requiring discontinuation. **- Unable to use -** 1. Behaviour: MACC Behavioural Adjustment Scale, observation of behaviour (results illegible).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided.
Allocation concealment (selection bias)	High risk	Medications were designated with an alphabetical code.
Blinding (performance bias and detection bias) All outcomes	Low risk	Neither raters nor participants were aware of the nature or quantity of drug given. Participants were given an identical number of capsules regardless of the individual dosage.
Incomplete outcome data (attrition bias) All outcomes	High risk	Two patients dropped out because of adverse events and were replaced by two reserve patients who had previously been receiving placebos.
Selective reporting (reporting bias)	High risk	Not all expected outcomes reported.
Other bias	Unclear risk	Funding not reported.

A +sulpiride 1994

Methods	**Allocation:** randomised. **Blinding:** open-label. **Duration:** 3 years. **Setting:** inpatients. **Country:** China.
Participants	**Diagnosis:** schizophrenia (CCMD-III). **N** = 105*. **Sex:** F 105..0 **Age:** 18-64 years, average ˜ 30 years. **History:** illness duration, range of 0.25-12 years, average ˜ 3 SD 3 years.
Interventions	1. **Combination therapy:** sulpiride (mean 911 SD 97 mg/day) + clozapine (84 SD 48 mg/day) (N = 36). 2. **Monotherapy:** clozapine (mean 265 SD 101 mg/day) (N = 34). 3. **Monotherapy:** sulpiride (mean 1077 SD 196 mg/day) (N = 35).
Outcomes	**- Usable data -** 1. Clinical response: no clinical improvement, relapse.

A +sulpiride 1994 *(Continued)*

	2. Adverse events: movement disorders. **-Unable to use -** 1. Leaving the study early (no information about the number who dropped out in each treatment group).
Notes	*Number of reported cases. Clozapine dosage was higher for the clozapine alone group. Abstract in English, report in Chinese.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Randomised into groups' without further detail.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label study.
Incomplete outcome data (attrition bias) All outcomes	High risk	5 people left the study early but no information about from which treatment group. Reasons for leaving early not described.
Selective reporting (reporting bias)	High risk	Not all expected outcomes reported.
Other bias	Unclear risk	Source of funding not reported.

A +trifluoperazine 1964

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 8 months. **Setting:** inpatients. **Design:** parallel. **Country:** USA.
Participants	**Diagnosis:** schizophrenia. **N** = 77. **Sex:** M 77. **Age:** not reported. **History:** chronic, most severely ill patients on the ward.
Interventions	1. **Combination therapy:** chlorpromazine + trifluoperazine (N = 27). 2. **Monotherapy:** chlorpromazine + placebo (N = 25). 3. **Monotherapy:** trifluoperazine + placebo (N = 25). **Schedule:** chlorpromazine 150 mg to 300 mg, trifluoperazine 5 mg to 10 mg. Lower dosage used for the first two months and then the higher dosage for the next 6 months.
Outcomes	**- Usable data -**

A +trifluoperazine 1964 *(Continued)*

1. Leaving the study early.
2. Clinical response: not clinically improved.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Assigned randomly to one of three drug groups and placed on a regimen of capsules and tablets.
Allocation concealment (selection bias)	Low risk	Both capsules containing these supplies were coded with colour labels to conceal the identity of the regimens but to permit administrator to increase dosage from one range to a higher one (after two months and six months) without disrupting the study.
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo capsules and placebo tablets matched the appearance of the capsules and tablets of the two drugs to insure no knowledge of which group was receiving which drug or drugs.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All included patients completed the trial.
Selective reporting (reporting bias)	High risk	Not all expected outcomes reported.
Other bias	Unclear risk	Source of support not reported.

B +any antipsychotic 2013

Methods

Allocation: randomised.

Blinding: single-blind.
Duration: 24 weeks*.
Setting: outpatient.

Design: parallel.

Country: Japan.

Participants

Diagnosis: schizophrenia (DSM-IV-TR).
N = 39.
Sex: M 19 F 16 (data from participants who ended the study).
Age: ~ 36 years.
History: chronic patients without acute exacerbation on a stable dose of 2 antipsychotics without prescription changes in the past 3 months.

Interventions

1. **Combination therapy:** continuing antipsychotics combination**
2. **Monotherapy:** switch to monotherapy, each participant and physician decided together which of the two antipsychotics to discontinue. Discontinuation had to occur within 12 weeks

Outcomes

- Usable data -

1. Mental state: PANSS (Total, Positive, Negative).
2. Adverse events: requiring discontinuation.

B +any antipsychotic 2013 *(Continued)*

	- Not usable data - 1. Leaving the study early (dates of discontinuation where not presented). **- Not used in this review -** 1. Brief Assessment of Cognition in Schizophrenia and the Life Assessment Scale for the Mentally Ill.
Notes	* From 0-12 weeks to discontinue polypharmacy, from 13-24 weeks to evaluate monotherapy versus combinations. ** The most common baseline polypharmacy combinations were risperidone and a first-generation antipsychotic (N =10), olanzapine and a first-generation antipsychotic (N = 9), olanzapine and risperidone (N = 5), risperidone and quetiapine (N = 3), olanzapine and aripiprazole (N = 3), aripiprazole and a first-generation antipsychotic (N = 3), quetiapine and aripiprazole (N = 2), blonanserin and a first-generation antipsychotic (N = 2), blonanserin and olanzapine (N = 1), blonanserin and quetiapine (N = 1). No protocol- a priori was published.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The patients were randomly divided into either the switching group or the continuing group using StatView.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	High risk	“For participants who were assigned to switch to monotherapy, each participant and physician decided together which of the two anti- psychotics to discontinue.” “The raters were blinded about which group the patients belonged to.”
Incomplete outcome data (attrition bias) All outcomes	High risk	Reasons for missing data differ in both group and this was not addressed in the data analysis.
Selective reporting (reporting bias)	Low risk	All measured outcomes were reported.
Other bias	Unclear risk	Supported by Grant in Ministry of Education, Culture, Sports, Science and Technology Japan.

B +aripiprazole 2008

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 16 week. **Setting:** outpatients. **Design:** parallel. **Country:** Europe, multi-centre.
Participants	**Diagnosis:** schizophrenia (DSM-IV-TR criteria). **N** = 207. **Sex:** M 134, F 73. **Age:** average ˜ 39 years.

B +aripiprazole 2008 *(Continued)*

	History: experienced at least 2.5 kg weight gain and sub-optimal efficacy and/or safety on clozapine.
Interventions	1. **Combination therapy:** aripiprazole + clozapine (N = 108). 2. **Monotherapy:** clozapine + placebo (N = 99). **Schedule:** aripiprazole 5 mg to 15 mg/day, stable dose of clozapine (163 mg to 900 mg/day).
Outcomes	**- Usable data -** 1. Leaving the study early. 2. Clinical response: GAF, CGI-I, CGI-S. 3. Mental state: PANSS. 4. Adverse events: serious or requiring discontinuation, weight gain, average weight gain, deaths, movement disorders. 5. Quality of Life: Subjective Well Being under Neuroleptics (SWN – short form). **- Not used in review -** 1. Investigator Assessment Questionnaire (IAQ), GEOPTE social cognition scale, ESS alertness scale, FSI fatigue scale, blood tests.
Notes	www.clinicaltrials.gov: NCT00300846

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule.
Allocation concealment (selection bias)	Low risk	"Randomization was achieved by a call-in interactive voice response system, from which a patient identification number was assigned."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Double-blind", no further details reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The LOCF method was used.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported.
Other bias	High risk	Supported by Bristol–Myers Squibb (Princeton, NJ, USA) and Otsuka Pharmaceutical Co., Ltd (Tokyo, Japan).

B +aripiprazole 2011

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 24 weeks. **Setting:** outpatient. **Design:** parallel. **Country:** Italy.
Participants	**Diagnosis:** schizophrenia (DSM-IV).

B +aripiprazole 2011 *(Continued)*

	N = 40. **Sex:** M 23, F 17. **Age:** 25 to 38 years. **History:** patients demonstrated persistent positive and negative symptoms despite an adequate trial of clozapine at the highest tolerable range (200 mg to 450 mg/day), for at least 1 year.
Interventions	1. **Combination therapy:** clozapine (200 mg to 450 mg/day) + aripiprazole (10 mg to 15 mg/day) (N = 20). 2. **Monotherapy:** clozapine (200 mg to 450 mg/day) + placebo (N = 20). **Schedule:** not reported
Outcomes	**- Usable data -** 1. Leaving the study early. 2. Mental state: BPRS. 3. Adverse events: movement disorders. **- Unable to use-** 1. Mental state: SANS, SAPS (Skewed data). **- Not used in review -** 1. Neurocogitive functioning: WCST; Neurocogitive functioning: the Verbal Fluency Task; Neurocogitive functioning: Stroop Colour-word Test, Calgary Depression Scale for Schizophrenia (CDSS).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation - automated system.
Allocation concealment (selection bias)	Low risk	During the study, the randomisation list was held securely, and released only after study completion.
Blinding (performance bias and detection bias) All outcomes	Low risk	Aripiprazole and placebo were dispensed in identical-appearing capsules; patients randomise to placebo took the same number of capsules as those assigned to aripiprazole.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"There were nine premature dropouts, six in the aripiprazole group and three in the placebo group. Of the aripiprazole group, three dropouts were due to concurrent illness, and three due to non-compliance with the visits. Of the placebo group, two dropouts were due to non-compliance and one changed his mind about participating in the study".
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported.
Other bias	Low risk	"No sponsor provided funding for this study".

B +pipotiazine 2002

Methods	**Allocation:** randomised (no further information). **Blinding:** not stated.

B +pipotiazine 2002 *(Continued)*

	Duration: 6 months. **Setting:** inpatients. **Design:** parallel. **Country:** China.
Participants	**Diagnosis:** chronic treatment resistant schizophrenia (CCMD-2-R). **N** = 84. **Age:** 27˜58 years. **Sex:** male and female. **Average length of illness:** 14.8 ± 11.4 years.
Interventions	1. **Combination therapy:** clozapine + pipotiazine: 50 mg of pipotiazine was given by intramuscular injection, after that 50 mg˜100 mg once every 4 weeks (N = unclear*). 2. **Monotherapy:** clozapine 200 mg˜450 mg/day (N = unclear*). **Schedule:** not reported
Outcomes	**-Usable data -** 1. Clinical response: not clinically improved* 2. Mental state: BPRS*. **- Unable to use -** 1. Adverse events: movement disorders (TESS) (no data reported).
Notes	*N assumed to be 42 in each treatment group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, no further information.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Author did not report on the number of people that completed the trial, thus we are unable to judge if there is incomplete outcome data.
Selective reporting (reporting bias)	High risk	TESS scores were measured, but not reported. Author only reported that there is no significant difference between groups.
Other bias	Low risk	None obvious.

B +quet/risp 2009

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 16 weeks.

B +quet/risp 2009 *(Continued)*

	Setting: outpatients. **Design:** parallel. **Country:** USA, multi-centre.
Participants	**Diagnosis:** schizophrenia or schizoaffective disorder (DSM-IV-TR). **N** = 323 **Sex:** M 198, F 125. **Age:** average ˜ 44 years. **History:** chronic, stable. Currently receiving a stable dose of quetiapine (400-800 mg/d) or risperidone (4 mg to 8 mg/day) for ≥4 weeks but with an inadequate response; must not have shown significant improvement or worsening of symptoms within 1 month of screening.
Interventions	1. **Combination therapy:** aripiprazole + quetiapine (N = 78). 2. **Combination therapy:** aripiprazole + risperidone (N = 90). 3. **Monotherapy:** quetiapine + placebo (N = 68). 4. **Monotherapy:** risperidone + placebo (N = 87). **Schedule:** aripiprazole 2-15 mg/d, quetiapine 400 mg to 800 mg/day, risperidone 4 mg to 8 mg/day.
Outcomes	**- Usable data -** 1. Leaving the study early. 2. Clinical response: not clinically improved. 3. Mental state: PANSS positive and PANSS negative. 4. Adverse events: serious or requiring discontinuation, weight gain, movement disorders, deaths. **- Unable to use -** 1. Global state: CGI (no SDs reported, no suitable mean to impute data). 2. Mental state: PANSS total score, MADRS (no SDs reported, no suitable mean to impute data). 3. Adverse events: AIMS, SAS, BAS, average weight gain, prolactin (no SDs reported, no suitable mean to impute data). 4. Quality of life: SWN (no SDs reported, no suitable mean to impute data). **- Not used in review -** 1. Calgary Depression Scale for Schizophrenia (CDSS), Arizona Sexual Experience Scale (ASEX), Fatigue Symptom Inventory (FSI), Brief Assessment of cognition in schizophrenia (BACS), Investigator's Assessment Questionnaire (IAQ), HDL, LDL, fasting glucose, triglycerides.
Notes	Trial Registration: clinicaltrials.cog Identifier: NCT00325689

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details provided.
Incomplete outcome data (attrition bias)	Low risk	All patients were analysed for safety. For efficacy analysis LOCF method was used.

B +quet/risp 2009 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	All expected outcomes reported.
Other bias	High risk	Supported by Bristol-Mywers Squibb (USA) and Otsuka Pharmaceutical Co (Japan)

B +risperidone 2010

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 16 weeks. **Setting:** inpatients and outpatients. **Design:** parallel. **Country:** USA.
Participants	**Diagnosis:** schizophrenia or schizoaffective disorder (DSM-IV). **N** = 69* **Sex:** M 44, F21. **Age:** average ~ 45 years. **History:** moderate illness severity and persistent psychosis despite adequate prior clozapine treatment.
Interventions	1. **Combination therapy:** risperidone + clozapine (N = 30). 2. **Monotherapy:** clozapine + placebo (N = 35). **Schedule:** risperidone 4 mg/day, clozapine dosage not reported.
Outcomes	**- Usable data -** 1. Leaving the study early. 2. Clinical response: CGI-S, CGI-I. 3. Mental state: BPRS, SANS. 4. Adverse events: serious or requiring discontinuation, prolactin level, average weight gain. **- Unable to use -** 1. Adverse events; AIMS, BAS, SAS. 2. Social functioning: LOF (No data reported). **- Not used in review -** 1. Cognitive scales, fasting glucose, DAI subjective response to treatment scale, vital signs.
Notes	*69 participants were randomised, 4 participants dropped out before the intervention started, 65 participants entered the active phase of the study. ClinicalTrials.gov Identifier: NCT00056498..

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomization was stratified by in-patient status", no further details provided.

B +risperidone 2010 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Double-blind", no further details provided for blinding of participants and personnel, raters were blinded to treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis was carried out and included all participants who received at least one dose of study medication.
Selective reporting (reporting bias)	Low risk	All expected outcomes reported.
Other bias	Unclear risk	Supported by a NIMH grant and a University of Maryland General Clinical Research Center grant, Janssen Pharmaceuticals provided study medication. ID: 551129.

B +sulpiride 1996

Methods	**Allocation:** randomised. Stratified randomisation using hospital admission time. **Blinding:** not stated. **Duration:** 3 months. **Setting:** inpatient. **Design:** parallel. **Country:** China.
Participants	**Diagnosis:** schizophrenia (DSM-II-R). **N** = 102. **Sex:** male and female. **Age:** 16-54 years. **Average length of illness:** mean ˜ 7 years, SD ˜ 4 years.
Interventions	1. **Combination therapy:** clozapine + sulpiride, 436.57 mg +\-89.85 mg, 1127.23 mg +\- 156.55 mg per day (N = 31). 2. **Monotherapy:** clozapine, 486.77 mg +\- 29.81 mg per day (N = 32). 3. **Monotherapy:** sulpiride, 1296.86 mg +\- 105.11 mg per day (N = 29). **Schedule:** not reported.
Outcomes	**- Usable data -** 1. Clinical response: not clinically improved. 2. Mental state: BPRS, SANS. 3. Adverse events: serious or requiring discontinuation. **- Unable to use -** 1. Leaving the study early (the treatment groups that participants dropped out from not reported). 2. Clinical response: CGI (Not reported). 3. Adverse events: TESS (Not reported).

B +sulpiride 1996 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Stratified randomisation using hospital admission time. No further information given.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described. Unclear if outcome assessment was blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	10 patients left the study early and were not included in the final analysis. The number lost to follow-up in each groups was not reported.
Selective reporting (reporting bias)	High risk	TESS and CGI scale scores were measured but not reported.
Other bias	Unclear risk	None obvious.

B +ziprasidone 2014

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 16 weeks. **Setting:** outpatients. **Design:** parallel. **Country:** Italy.
Participants	**Diagnosis:** schizophrenia (DSM-IV). **N** = 40. **Sex:** M 13, F 27. **Age:** ~ 35 years. **History:** chronic, treatment resistant patients that demonstrated persistent positive and negative symptoms despite an adequate trial of clozapine.
Interventions	1. **Combination:** clozapine (350 mg to 600 mg/day) + ziprasidone (80 mg/day) (N = 20). 2. **Monotherapy:** clozapine (350 mg to 600 mg/day) + placebo (N = 20).
Outcomes	**- Usable data -** 1. Leaving the study early. 2. Mental State: PANSS (Total), BPRS. 3. Adverse event: requiring discontinuation. **- Not able to use -** 1. Mental state: PANSS (Positive, Negative) (Skewed data). 2. Adverse event: white blood cell count (No data reported).

B +ziprasidone 2014 *(Continued)*

- Not used in this review -

1. CDSS (Calgary Depression Scale for Schizophrenia).

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Prerandomized codes generated by computer."
Allocation concealment (selection bias)	Low risk	"Coded treatments were allocated sequentially to subjects in order of their registration for the trial. The randomization list was held securely."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"None of the research personnel, who enrolled, assessed, and treated the patients, were aware of the patient assignments until the study was concluded. Ziprasidone and placebo were dispensed in identical-appearing capsules; patients randomized to placebo took the same number of capsules as those assigned to ziprasidone."
Incomplete outcome data (attrition bias) All outcomes	High risk	"Two discontinuations in the ziprasidone group were all attributed to treatment-emergent adverse events (akathisia and sedation) and 2 withdrew for perceived lack of efficacy. Among a total of 3 dropouts in the placebo group, 2 were due to non-compliance with the visits and 1 withdrew due to a subjectively assessed lack of efficacy." The reasons for leaving the study early differ across groups. "An intention-to-treat analysis with last-observation-carried forward was performed."
Selective reporting (reporting bias)	High risk	No protocol available. "No clinically significant changes" reported for haematological parameters.
Other bias	Low risk	None obvious.

C +amisulpride 2008

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 6 weeks. **Setting:** inpatients. **Design:** parallel. **Country:** Germany.
Participants	**Diagnosis:** schizophrenia (DSM-IV - 295.32; 295.34). **N** = 16. **Sex:** M 12, F 4. **Age:** average ~ 43 years. **History:** chronically ill, had already received clozapine for at least three months on a stable dose and were only partially or even non-respondent.
Interventions	1. **Combination therapy:** clozapine 300 mg/day + amisulpride 400 mg/day (N = 7). 2. **Combination therapy:** clozapine 300 mg/day + amisulpride 600 mg/day (N = 6). 3. **Monotherapy:** clozapine 300 mg/day + placebo (N = 3).

C +amisulpride 2008 *(Continued)*

	Schedule: not reported.
Outcomes	**- Usable data -** 1. Leaving the study early. 2. Adverse events: serious or requiring discontinuation. 3. Adverse events: tremor. **- Unable to use -** 1. Global state: CGI-S, GAF (no SD reported, not able to impute as no similar means). 2. Mental state: BPRS, (no SD reported, not able to impute as no similar means). 3. Change on prolactin level (no SD reported, not able to impute as no similar means). 4. Adverse events: Extrapyramidal Symptom Rating Scale (ESRS; no data reported). 5. Quality of life: self rated health questionnaire (SF-36; no data reported). **- Not used in review -** 1. Montgomery Asberg Depression Rating Scale (MADRS), pulse and blood pressure, laboratory results, ECG, physical and neurological examinations.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	Two patients from combination group and one from monotherapy did not complete study because of lack of efficacy and unknown reasons.
Selective reporting (reporting bias)	High risk	Not all expected outcomes reported.
Other bias	High risk	Not all patients suggested from sample size calculation were recruited. Protocol not published. Study supported by Sanofi-Synthelabo.

C +arip/pali 2014

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 6 weeks. **Setting:** outpatient. **Design:** parallel.

C +arip/pali 2014 *(Continued)*

	Country: India.
Participants	**Diagnosis:** Schizophrenia (DSM-IV). **N** = 90. **Sex:** * **Age:** ~ 36 years. **History:** Receiving olanzapine for at least 6 weeks and showing partial or no response to PANSS Scale..
Interventions	1. **Combination therapy:** olanzapine (10 mg) + aripiprazole (10 mg) (N = 30). 2. **Combination therapy:** olanzapine (10 mg) + paliperidone (3 mg) (N = 30). 3. **Monotherapy:** olanzapine (3 mg to 6 mg) + placebo (N = 30).
Outcomes	**- Usable data -** 1. Leaving the study early. 2. Mental State: PANSS total. **- Not used in this review -** 1. Digit symbol substitution test, six digit cancellation test, critical flicker fusion test, arithmetic ability, verbal fluency test, digit span test, hand steadiness test, finger tapping test.
Notes	No clinical registration.. Funding: no funding sources. Conflict of interest: none declared. * The gender of the participants in the monotherapy group does not correspond to the number of participants included in the trial. No response when we tried contacting the author to clarify this issue.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomized treatment allocation sequence was generated by statistician using random number table."
Allocation concealment (selection bias)	Low risk	"The code of this random allocation sequence was retained in the sealed envelope by this person and was opened only after the completion of study during analysis of data."
Blinding (performance bias and detection bias) All outcomes	Low risk	"Double blinding was done by inserting aripiprazole or paliperidone or placebo tablet in a non-transparent capsule." "It was handed over along with identical plastic containers filled with the study drugs (45 capsules each of aripiprazole or paliperidone or placebo) to a third person not directly involved in this study." "The patient as well as the investigator was unaware of the treatment being administered."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All the randomized patients in each group have satisfactorily completed the study."
Selective reporting (reporting bias)	Low risk	All outcomes reported in methods are presented in the results.
Other bias	High risk	Baseline imbalance in PANSS (total) values.

C +aripiprazole 2007

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 9 weeks. **Setting:** inpatients. **Design:** parallel. **Country:** China.
Participants	**Diagnosis:** schizophrenia. **N** = 61. **Sex:** M 61. **Age:** 18-50 years, average ~ 35 years. **History:** treated with sulpiride for 6 weeks prior to the study.
Interventions	1. **Combination therapy:** sulpiride 600 mg to 900 mg + aripiprazole 10 mg (N = 31). 2. **Monotherapy:** sulpiride 500 mg to 900 mg (N = 30). **Schedule:** daily dose.
Outcomes	**- Usable data -** 1. Adverse events: movement disorders, TESS and prolactin.
Notes	*Abstract in English, article in Chinese.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised (no further information provided).
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete data.
Selective reporting (reporting bias)	High risk	Not all expected outcomes reported.
Other bias	Unclear risk	No information about source of funding.

C +aripiprazole 2007b

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 8 weeks. **Setting:** not reported. **Design:** parallel.

C +aripiprazole 2007b *(Continued)*

	Country: USA.
Participants	**Diagnosis:** schizophrenia (DSM-IV). **N** = 56. **Sex:** M 22, F 32. **Age:** average ˜ 39 years. **History:** treated with haloperidol monotherapy and were taking the same dosage of haloperidol for at least 3 months.
Interventions	1. **Combination therapy:** aripiprazole + haloperidol (N = 26). 2. **Monotherapy:** haloperidol + placebo (N = 28). **Schedule:** aripiprazole dose fixed at 15 mg/day for first four weeks, then 30 mg/day for following four weeks, haloperidol dose remained fixed throughout study.
Outcomes	**- Usable data -** 1. Leaving the study early. 2. Clinical response: CGI-S. 3. Mental state: BPRS, SANS. 4. Adverse events: serious or requiring discontinuation, drowsiness. **- Unable to use -** 1. Adverse events: prolactin, BAS, SAS (Skewed data).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	No ITT analysis performed.
Selective reporting (reporting bias)	High risk	Not all expected outcomes reported.
Other bias	Unclear risk	Supported by a grant from the Korea Health R&D Project, Ministry of Health and Welfare, and Republic of Korea (0412-CT02-0704-0006).

C +aripiprazole 2008

Methods	**Allocation:** randomised. **Blindning:** double-blind. **Duration:** 8 weeks.

C +aripiprazole 2008 *(Continued)*

	Setting: inpatients and outpatients. **Design:** parallel. **Country:** Korea.
Participants	**Diagnosis:** schizophrenia (DSM-IV). **N** = 61. **Sex:** M 48, F 13. **Age:** average ˜ 32 years. **History:** treatment failure prior to clozapine; clozapine treatment for more than 1 year with at least 8 weeks at a stable daily dose of 400 mg or more; no change in clozapine daily dose or other concomitant medication for more than 3 months.
Interventions	1. **Combination therapy:** clozapine + aripiprazole (N = 30). 2. **Monotherapy:** clozapine + placebo (N = 32). **Schedule:** clozapine 400 + mg/day, aripiprazole 5 mg to 30 mg/day.
Outcomes	**- Usable data -** 1. Leaving the study early. 2. Clinical response: CGI-S. 3. Mental state: BPRS, SANS. 4. Adverse events: serious or requiring discontinuation, weight gain, prolactin level, DIEPSS, UKU. **- Unable to use -** 1. UKU (no means and SDs reported). 2. Prolactin level (Skewed data). 3. White blood cell count (Not reported). **- Not used in review -** 1. Montgomery-Asberg Depression Rating Scale (MADRS), Yale-Brown Obsessive Compulsive Scale (YBOCS), vital signs (pulse rate and systolic/diastolic blood pressure),ECG, liver function tests, measurement of electrolyte levels, urinalysis, fasting blood sugar, 2-hour postprandial blood sugar, total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol.
Notes	*LOCF method was used for any patients who did not complete the 8-week double-blind phase. Trial Registration: clinicaltrials.gov Identifier: NCT00328367

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random-numbers chart in blocks of 4. The allocation sequence was generated and monitored by faculty members who were not involved in any part of this study.
Allocation concealment (selection bias)	Low risk	The investigators were not involved in any part of this study. The investigators were unaware of the block size.
Blinding (performance bias and detection bias) All outcomes	Low risk	All the participants and investigators remained blind throughout the study, and the data analyses were also performed by investigators blind to the identity of the participants.
Incomplete outcome data (attrition bias) All outcomes	Low risk	One patient with a history of arteriovenous malformation was mistakenly included in the random assignment to aripiprazole and was consequently ex-

C +aripiprazole 2008 *(Continued)*

		cluded from the itt analysis. LOCF method was used for any patients who did not complete the 8-week double-blind phase.
Selective reporting (reporting bias)	Low risk	All planned outcomes reported except for the one person who dropped out.
Other bias	High risk	Funded by the Ministry of Science and Technology, Republic of Korea, and partly by a research grant from Korea Otsuka Pharmaceutical to Dr. Y. S. Kim.

C +aripiprazole 2008b

Methods	**Allocation:** randomised (using random number table). **Blinding:** not stated. **Duration:** 6 weeks. **Setting:** community and inpatients. **Design:** parallel. **Country:** China.
Participants	**Diagnosis:** schizophrenia (in remission, BPRS score < 25), diagnosed with CCMD-3. **N** = 80. **Age:** 18-52 years. **Sex:** male and female. **History:** average length of illness: aripiprazole group, median = 7.8 years, range = 0.2 to 22 years; chlorpromazine group = not stated; placebo group, median = 9.4 years, range = 0.1 to 18 years.
Interventions	1. **Combination therapy:** aripiprazole (5 mg/day) + chlorpromazine (200 mg˜450 mg/day) (N = 40). 2. **Monotherapy:** placebo + chlorpromazine (200 mg˜450 mg/day) + placebo (100 mg/day) (N = 40).
Outcomes	**- Usable data -** 1. Mental state: BPRS. 2. Adverse events: prolactin level, drowsiness.
Notes	Article in Chinese.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised using random number table.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is unclear if there are incomplete data.

C +aripiprazole 2008b *(Continued)*

Selective reporting (reporting bias)	High risk	TESS score was measured, but not reported.
Other bias	Low risk	None obvious.

C +aripiprazole 2009

Methods	**Allocation:** randomised (no further information). **Blinding:** single-blind. **Duration:** 6 weeks. **Setting:** community patients. **Design:** parallel. **Country:** China.
Participants	**Diagnosis:** schizophrenia (CCMD-3). **N** = 60. **Sex:** male and female. **Age:** mean ~ 33.5 years, SD ~ 12 years. **History**: length of illness mean ~ 15 months, SD ~ 9.5 years, stage of illness in remission, BPRS score < 25, have been receiving haloperidol treatment for > 6 months, prolactin > 60 ug/L, no other severe physical illness.
Interventions	1. **Combination therapy:** haloperidol plus aripiprazole (5 mg per capsule, one capsule per day for 6 months) (N = 30). 2. **Monotherapy:** haloperidol plus placebo (vitamin C 100 mg per capsule, one capsule per day for 6 month) (N = 30). **Schedule:** not reported.
Outcomes	**- Usable data -** 1. Mental state: BPRS. 2. Adverse events: prolactin level, drowsiness.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, but no further information.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Single-blind, untested.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome data.

C +aripiprazole 2009 *(Continued)*

Selective reporting (reporting bias)	High risk	TESS score was measured, but not reported.
Other bias	Low risk	None obvious.

C +aripiprazole 2012

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 12 weeks. **Setting:** outpatient. **Design:** parallel. **Country:** Japan.
Participants	**Diagnosis:** schizophrenia (DSM-IV). **N** = 36. **Sex:** M 12, F 24. **Age:** average 35.3. **History:** no details.
Interventions	1. **Combination therapy:** risperidone (2 mg to 12 mg/day) + aripiprazole (6 mg to 30 mg/day) OR olanzapine (2.5 mg to 20 mg/day) + aripiprazole (6 mg to 30 mg/day) (N = 18). 2. **Monotherapy:** risperidone (2 mg to 12 mg/day) + placebo OR olanzapine (2.5 mg to 20 mg/day) + placebo (N = 18).
Outcomes	**- Usable data -** 1. Mental state: PANSS. **- Unable to use -** 1. Adverse events: PANSS positive, UKU (Skewed data). **- Not used in review -** 1. Neurocognitive outcome: Brief Assessment of Cognition in Schizophrenia (BACS).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, no further details.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Patients were evaluated by the same investigator. This investigator was from a different hospital and was not involved in patient care. In addition, the investigator was blind to drug regimens and the drug concentrations. However, he had access to the nursing charts." No details as to blindness of participants and personnel other than "double-blind".
Incomplete outcome data (attrition bias)	Unclear risk	No information provided.

C +aripiprazole 2012 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported.
Other bias	Low risk	Funded by the Hirosaki Research Institute for Neurosciences.

C +aripiprazole 2013

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 8 weeks. **Setting:** outpatient. **Design:** parallel. **Country:** USA.
Participants	**Diagnosis:** schizophrenia or schizoaffective disorder (DSM-IV). **N** = 38. **Sex:** M 22, F 8. (Only reported the group that completed the 8 weeks). **Age:** ~ 44 years. **History:** treatment with clozapine for at least 1 year and on a stable dose of for at least 1 month. Stratified by the presence or absence of diabetes.
Interventions	1. **Combination therapy:** clozapine (Mean = 397 mg/day) + aripiprazole (15 mg/day) (N = 20). 2. **Monotherapy: c**lozapine (Mean = 400 mg/day) + placebo (N = 18).
Outcomes	**- Usable data -** 1. Leaving the study early. 2. Mental state: PANSS. 3. Adverse event: drowsiness, weight gain. **- Not able to use -** 1. Adverse event: AIMS, SAS (Not reported). **- Not used in this review -** 1. Fasting plasma glucose, Fasting serum insulin, homeostasis model of assessment of insulin resistance; haemoglobin A1c; insulin sensitivity index (SI); glucose effectiveness (SG); acute insulin response to glucose, disposition index, HDL, LDL, VLDL and anthropometric assessment.
Notes	ClinicalTrials.gov identifier NCT00345033.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“Randomized” No other information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.

C +aripiprazole 2013 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Double blind" No other information provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	The analysis does not account for the losses.
Selective reporting (reporting bias)	High risk	Results for SAS and AIMS were reported on methods but do not have published results.
Other bias	Low risk	Funded by National Institutes of Health and by National Center for Research Resources General Clinical Research Centers Program.

C +aripiprazole 2013b

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 24 weeks (first 12 weeks using antipsychotic combinations). **Setting:** inpatient. **Design:** parallel. **Country:** Korea, multi-centre.
Participants	**Diagnosis:** schizophrenia (DSM-IV-TR). **N** = 35. **Sex:** M 26, F 9. **Age:** ~ 50 years. **History:** Chronic participants**,** stabilized on their current dose of risperidone (3 mg to 6 mg/day) for a minimum of 3 months prior to enrolment in the study.
Interventions	1. **Combination therapy:** risperidone (3 mg to 6 mg) + aripiprazole (10 mg/day) for 12 weeks (N = 17). From weeks 13 to 24 participants in the combination group received aripiprazole and tapered risperidone. 2. **Monotherapy:** risperidone (3 mg to 6 mg) + placebo for 12 weeks (N = 18). From weeks 13 to 24 participants in the the monotherapy group received their current risperidone dose without placebo.
Outcomes	**- Not usable data -** 1. Mental state: PANSS (Skewed data). 2. Adverse events: ESRS (Skewed data). 3. Leaving the study early (Presented only at 24 weeks). 4. Adverse events: requiring discontinuation, prolactin levels (Presented only at 24 weeks).
Notes	No clinical registration, no information regarding funds and no declaration of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned". No other information provided

C +aripiprazole 2013b *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No other information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Double-blind". No further details
Incomplete outcome data (attrition bias) All outcomes	Low risk	For missing data, the LOCF analysis was used.
Selective reporting (reporting bias)	Low risk	All outcome reported in methods, were presented.
Other bias	Unclear risk	Non detected.

C +aripiprazole 2014

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 8 weeks. **Setting:** unclear. **Design:** parallel. **Country:** China.
Participants	**Diagnosis:** schizophrenia (ICD-10) **N** = 116 **Age:** ~ 34 **Sex:** M 54, F62 **History:** Use of stable dose of risperidone (3 mg to 8 mg/day) monotherapy for at least 6 months.
Interventions	1. **Combination therapy:** risperidone (3 mg to 8 mg/day) + aripiprazole (10 mg to 20 mg/day) (N = 59) 2. **Monotherapy:** risperidone (3 mg to 8 mg/day) + placebo (N = 57)
Outcomes	**- Usable data -** 1. Leaving the study early 2. Clinical response: CGI-S 3. Mental state: PANSS 4. Adverse events: requiring discontinuation **- Not able to use -** 1. Adverse events: Prolactin levels (Skewed data)
Notes	Abstract in English, report in Chinese.

Risk of bias

Bias	Authors' judgement	Support for judgement

C +aripiprazole 2014 *(Continued)*

Random sequence generation (selection bias)	Low risk	From correspondence: "Random numbers table is used for randomization."
Allocation concealment (selection bias)	Low risk	From correspondence: "Central telephone randomization system."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind. Placebo, which have the same colour, shape and taste with aripiprazole.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT.
Selective reporting (reporting bias)	Low risk	All measured outcomes were reported.
Other bias	High risk	Supported by Chendu Kanghong Pharmaceutical company

C +aripiprazole 2015

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 8 weeks. **Setting:** Inpatient and outpatient. **Design:** parallel. **Country:** China.
Participants	**Diagnosis:** The diagnosis of schizophrenia was determined by the Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version. **N** = 119. **Sex:** M 58, F 61. **Age:** average 33.5. **History:** Chronic participants, stable during the screening phase, as indicated by a total score < 70 on the Positive and Negative Syndrome Scale (PANSS) and had to experience hyperprolactinaemia induced by risperidone.
Interventions	1. **Combination therapy:** risperidone (mean = 4.63 mg/day) + aripiprazole (5 mg) (N = 30). 2. **Combination therapy:** risperidone (mean = 4.79 mg/day) + aripiprazole (10 mg) (N = 29). 3. **Combination therapy:** risperidone (mean = 5.07 mg/day) + aripiprazole (15 mg) (N = 30). 4. **Monotherapy:** Risperidone (mean = 4.93 mg/day) + Placebo (N = 30).
Outcomes	**- Usable data -** 1. Leaving the study early. 2. Clinical response: CGI-S. 3. Adverse events: requiring discontinuation. **- Unable to use -** 1. Mental state: PANSS (Skewed data). 2. Adverse events: prolactin levels, BAS and SAS (Skewed data). **- Not used in review -**

C +aripiprazole 2015 *(Continued)*

1. Body weight, waist circumference, hip circumference, fasting glucose, triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol and QTc interval.

Notes	Data from correspondence used for 'Risk of bias' assessment. Trial Registration: clinicaltrials.gov Identifier: NCT02013232 .

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	From correspondence: "Random numbers table is used for randomization."
Allocation concealment (selection bias)	Low risk	From correspondence: "Central telephone randomization system."
Blinding (performance bias and detection bias) All outcomes	Low risk	"Double-blind" "Placebo and aripiprazole tablets were physically indistinguishable."
Incomplete outcome data (attrition bias) All outcomes	Low risk	“Among the 12 non-completers (10.1%), 4 had been assigned to placebo, 2 to 5 mg/day of aripiprazole, 2 to 10mg/day of aripiprazole, and 4 to 20mg/day of aripiprazole. Of these, 7 (5.9%) were lost to follow-up, 2 (1.7%) withdrew consent, 3 (2.5%) withdrew because of adverse event” “Using data from all randomized patients with at least 1 follow-up test (modified intent-to treat analysis).”
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported.
Other bias	High risk	This study was supported from Funding for Beijing Outstanding Talent Training Projects, China. Kanghong Pharmaceutical provided the medication and placebo.

C +aripiprazole 2015b

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 8-weeks. **Setting:** outpatient. **Design:** parallel. **Country:** India.
Participants	**Diagnosis:** schizophrenia (DSM-IV). **N** = 30. **Sex:** M 15, F 15. **Age:** ~ 32 years.

C +aripiprazole 2015b *(Continued)*

	History: participants on a stable dose of risperidone.
Interventions	1. **Combination therapy:** risperidone (median = 6 mg) + aripiprazole (10 mg/day) (N = 15). 2. **Monotherapy:** risperidone (median = 6 mg) + placebo (N = 15).
Outcomes	**- Usable data -** 1. Leaving the study early. 2. Adverse event: BAS. **- Unable to use -** 1. Metal state: BPRS* (Skewed data). 2. Adverse event: prolactin levels*, SAS* (Skewed data). **- Not used in review -** 1. Galactorrhoea 2. Arizona sexual experience scale 3. Prolactin-related symptoms
Notes	Funding by: Indian Medical Council of Research (ICMR), India. * Unpublished data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated randomisation schedule using permuted blocks of random sizes, generated at the pharmacy."
Allocation concealment (selection bias)	Low risk	"Allocation concealment was ensured as the randomisation code was not released until all the recruitment and assessments were completed"
Blinding (performance bias and detection bias) All outcomes	Low risk	"placebo tablets that were identical to the aripiprazole tablets..." AND "The investigators, participants and their carers were masked to the medications throughout the study..."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reasons for dropouts not reported.
Selective reporting (reporting bias)	Low risk	No mean and SD reported for BPRS, prolactin levels, and SAS; data obtained through correspondence.
Other bias	Low risk	Concern about baseline imbalances in prolactin levels, but this outcome was not used in the analysis.

C +aripiprazole 2015c

Methods	**Allocation:** randomised. **Blinding:** open-label. **Duration:** 8-weeks. **Setting:** inpatient and outpatient. **Design:** parallel.

C +aripiprazole 2015c *(Continued)*

	Country: China.
Participants	**Diagnosis:** Schizophrenia or schizoaffective disorder (DSM-IV). **N** = 113. **Sex:** M 46, F 67. **Age:** ~ 30 years. **History:** Stable patients with elevated serum prolactin level (> 324 mIU/L in males and > 496 mIU/L in females).
Interventions	1. **Combination therapy:** risperidone (4 mg to 6 mg/ day) + aripiprazole (10 mg/day) (N = 56). 2. **Monotherapy:** risperidone (4 mg to 6 mg/ day) (N = 57).
Outcomes	**- Usable data -** 1. Leaving the study early. 2. Adverse events: requiring discontinuation, any movement disorders. **- Not able to use -** 1. Mental state: PANSS Total*, PANSS Positive*, PANSS Negative* (Skewed data). 2. Adverse events: prolactin levels** (Skewed data), BAS (Not reported), UKU (Not reported). 3. Rating Scale for Extrapyramidal Side Effects** (Not reported).
Notes	* Extracted from a graph. ** This scale corresponds to SAS. Chinese Clinical Trial Registry: ChiCTR-IOR-15006278.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	From the protocol: “The generation of random sequence by method of random number table”.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	High risk	“Open-label trial”.
Incomplete outcome data (attrition bias) All outcomes	High risk	Reason for leaving the study early differ between groups. Only participants that completed the trial were included for the analysis.
Selective reporting (reporting bias)	High risk	No mean and SD reported for BAS, UKU and SAS.
Other bias	Low risk	Funding by the National Natural Science Foundation of China and the Natural Science Foundation of Henan.

C +aripiprazole 2016

Methods	**Allocation:** randomised. **Blinding:** open-label. **Duration:** 8-weeks. **Setting:** inpatient. **Design:** parallel. **Country:** China.
Participants	**Diagnosis:** schizophrenia (DSM-IV). **N** = 60. **Sex:** M 0, F 60. **Age:** average 33.3 years. **History:** Female participants were randomised if they presented hyperprolactinaemia (> 496 mIU/L) and a decrease in the PANSS score by > 50%. Previous to randomisation participants received risperidone or paliperidone treatment combined with modified electroconvulsive therapy (if antipsychotic drug treatment was not effective).
Interventions	1. **Combination therapy:** paliperidone (6 mg to 12 mg/day) + aripiprazole (5 mg) (N = 11). 2. **Combination therapy:** risperidone (3 mg to 6 mg/day) + aripiprazole (5 mg) (N = 19). 3. **Monotherapy:** paliperidone (6 mg to 12 mg/day) (N = 16). 4. **Monotherapy:** risperidone (3 mg to 6 mg/day) (N = 14).
Outcomes	**- Usable data -** 1. Leaving the study early. 2. Mental state: PANSS Total. 3. Adverse events: requiring discontinuation, any movement disorders. **- Not able to use -** 1. Mental state: PANSS Positive and negative (Skewed data). 2. Adverse events: prolactin levels (Not able to impute), TESS (Not reported), weight gain (Not reported). **- Not used in this review -** 1. Estradiol levels.
Notes	Chinese clinical trial register: ChiCTR-TRC-14004186. Funding by: Shanghai Natural Science Research Foundation, National Key Clinical Disciplines at Shanghai Mental Health Center, and Shanghai Clinical Center for Mental Disorders.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	From the protocol: “Using SAS9.3 version software and making block randomization with PROC PLAN process”.
Allocation concealment (selection bias)	Unclear risk	No information provided.

C +aripiprazole 2016 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	High risk	Open-label trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"five participants were lost during follow-up in the treatment group. In the control group, two participants were lost during the follow-up and withdrew because of adverse events."
Selective reporting (reporting bias)	High risk	The outcomes mentioned in the protocol differ from those presented in the published report.
Other bias	High risk	Baseline imbalances in PANSS values.

C +clozapine 2001

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 8 weeks. **Setting:** inpatients. **Design:** parallel. **Country:** China.
Participants	**Diagnosis:** schizophrenia. **N** = 40. **Sex:** M and F (not reported). **Age:** average ~ 32 years. **History:** not clear.
Interventions	1. **Combination therapy:** risperidone 4 mg to 6 mg + clozapine 50 mg to 300 mg (N = 20). 2. **Monotherapy:** risperidone 4 mf to 6 mg (N = 20). **Schedule:** daily dose.
Outcomes	**- Usable data -** 1. Leaving the study early. 2. Clinical response: not clinically improved. 3. Mental state: BPRS. 4. Adverse events: movement disorders, drowsiness.
Notes	*Abstract in English, report in Chinese.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Sequential trial randomisation".
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information provided.

C +clozapine 2001 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All included patients completed the trial.
Selective reporting (reporting bias)	High risk	Not all expected outcomes reported.
Other bias	Unclear risk	No source of funding reported.

C +clozapine 2013

Methods	**Allocation:** randomised. **Blinding:** unclear. **Duration:** 8 weeks. **Setting:** inpatient. **Design:** parallel. **Country:** China.
Participants	**Diagnosis:** schizophrenia (CCMD-3). **N** = 50. **Sex:** M 23 , F 27. **Age:** ~ 34 years. **History:** Chronic participants with predominantly negative symptoms.
Interventions	1. **Combination therapy:** any antipsychotic* + clozapine (orally disintegrated tablet) (300 mg to 400 mg/day) (N = 25). 2. **Monotherapy:** any antipsychotic** (N = 25).
Outcomes	**- Usable data -** 1. Clinical response: not clinically improved. 2. Leaving the study early. 3. Adverse events: drowsiness. **- Not usable data -** 1. Mental state: PANSS (Total, Negative) (Skewed data).
Notes	* quetiapine fumarate (N = 6), ziprasidone (N = 6), risperidone (N = 5), aripiprazole (N = 4), sulpiride (N = 4). **quetiapine fumarate (N = 6), ziprasidone (N = 5), risperidone (N = 6), aripiprazole (N = 4), sulpiride (N = 4). Abstract in English, report in Chinese.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified.

C +clozapine 2013 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not specified.
Blinding (performance bias and detection bias) All outcomes	High risk	Not specified.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All included participants completed the trial.
Selective reporting (reporting bias)	Low risk	All outcomes were reported.
Other bias	Low risk	None obvious

C +CPZ 1973

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 30 days. **Setting:** inpatients. **Design:** parallel. **Country:** China.
Participants	**Diagnosis**: 75% of the participants likely to be chronic schizophrenia patients with an acute episode. **N** = 46. **Sex:** M 24, F 22. **Age:** average ~ 37 years. **History:** acute psychotics recently admitted to the two health centres, required antipsychotic medication.
Interventions	1. **Combination therapy:** fluphenazine enanthate + chlorpromazine (N = 15). 2. **Monotherapy:** fluphenazine enanthate (N = 16). 3. **Monotherapy:** chlorpromazine (N = 15). **Schedule (on average):** fluphenazine enanthate 26 mg every 11.5 days + chlorpromazine 349.6 mg/day, fluphenazine enanthate 28.5 mg every 11.5 days, chlorpromazine 388 mg/day. Doses administered at clinically determined intervals.
Outcomes	**- Usable data -** 1. Clinical response: not clinically improved. 2. Adverse events: movement disorders. **- Unable to use -** 1. Behaviour: Nurses Observation Scale for Inpatient Evaluation (NOSIE; no data reported).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

C +CPZ 1973 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	At both centres, all patients involved in the study had their dosage regulated by the usual clinical staff. The research psychiatrist at each centre scrupulously avoided influencing the amount or frequency of administration of antipsychotic medication used during the course of the study, except to specify that fluphenazine enanthate dosage should not exceed 75 mg in a single dose.
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 50% of the patients from each treatment group were discharged (lost to follow-up) within 30 days after admission.
Selective reporting (reporting bias)	High risk	Not all expected outcomes reported.
Other bias	Unclear risk	Funding not reported.

C +CPZ 1989

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 8 weeks. **Setting:** inpatients. **Design:** parallel. **Country:** China.
Participants	**Diagnosis:** schizophrenia (DSM-III). **N** = 57. **Sex:** M 35, F 22. **Age:** average ˜ 31 years. **History:** not reported.
Interventions	1. **Combination therapy:** chlorpromazine + clozapine (N = 20). 2. **Monotherapy:** chlorpromazine (N = 20). 3. **Monotherapy:** clozapine (N = 17). **Schedule:** chlorpromazine 100-600 mg, clozapine 50 mg to 600 mg, combination therapy maximum of either was 400 mg.
Outcomes	**- Usable data -** 1. Mental state: BPRS. **- Not used in review -** 1. Plasma homovanillic acid (HVA) levels.
Notes	Data extrapolated from figure 2.

Risk of bias

Bias	Authors' judgement	Support for judgement

C +CPZ 1989 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Weekly BPRS by psychiatrists blind to medication over 8 weeks. No further details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details provided.
Selective reporting (reporting bias)	High risk	Not all expected outcomes reported.
Other bias	Unclear risk	Funding not reported.

C +CPZ 1999

Methods	**Allocation:** 'randomised' according to hospital admission order. **Blinding:** not stated. **Duration:** 6 weeks. **Setting:** inpatients. **Design:** parallel. **Country:** China.
Participants	**Diagnosis:** schizophrenia (CCMD-2-R). **N** = 115. **Age:** mean ˜ 28 years, SD ˜ 10 years. **Sex:** male and female. **History:** length of illness mean ˜ 11 months, SD ˜ 9 months.
Interventions	1. **Monotherapy:** chlorpromazine (400 mg/day) (N = 35). 2. **Monotherapy:** clozapine (300 mg/day) (N = 40). 3. **Combination therapy:** chlorpromazine (100 mg/day)+ clozapine (300 mg/day) (N = 40).
Outcomes	**- Usable data -** 1. Mental state: BPRS. 2. Adverse events: TESS.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	'Randomised' according to hospital admission order, but no further information.

C +CPZ 1999 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome data.
Selective reporting (reporting bias)	Low risk	All measured outcomes were reported.
Other bias	Low risk	None obvious.

C +fluphen dec 2009

Methods	**Allocation:** randomised 1:1 ratio. **Blinding:** double-blind. **Duration:** 12 weeks. **Setting:** inpatients. **Design:** parallel. **Country:** Iran.
Participants	**Diagnosis:** schizophrenia (DSM). **N** = 28. **Sex:** females only. **History:** poor response to olanzapine, chronic schizophrenia.
Interventions	1. **Combination therapy:** Olanzapine plus fluphenazine decanoate (N = 14). 2. **Monotherapy:** Olanzapine plus placebo (N = 14). **Schedule:** olanzapine 15 mg to 25 mg daily, fluphenazine decanoate week zero 6.25 mg/2 weeks IM, and increased by 6.25 mg increments, as needed or tolerated, in biweekly intervals, to a maximum of 25 mg/2 weeks by week eight.
Outcomes	**- Usable data -** 1. Leaving the study early. 2. Clinical response: CGI-S. 3. Mental state: SAPS, SANS. 4. Adverse events: serious or requiring discontinuation, SAS. **- Not used in review -** 1. Schedule for Assessment of Insight (SAI).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

C +fluphen dec 2009 *(Continued)*

Random sequence generation (selection bias)	High risk	Quasi-randomised "Randomly entered in one of the two matching contemporaneous groups, alternately one patient after the other (one into the experiment group and the next into the control group, in sequence and back-to-back)."
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding (performance bias and detection bias) All outcomes	Low risk	"Double-blind". "The placebo had been arranged in the shape of comparable vials, like the target drug". "The evaluators, as well, were unaware concerning the partition and the type of medications arranged for each group."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported.
Selective reporting (reporting bias)	High risk	Not all expected outcomes reported.
Other bias	Unclear risk	Funding not reported.

C +haloperidol 2006

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 10 weeks.
Participants	**Diagnosis:** schizophrenia (criteria not reported). **N** = 10. **Sex:** not reported. **Age**: not reported. **History:** Treatment-resistant schizophrenia, resistant to 2 adequate trials with 2 different antipsychotics and to a trial with clozapine during a minimum of 6-8 weeks in adequate dosage.
Interventions	1. **Combination therapy:** clozapine (mean 450 mg/day SD 70.7) + haloperidol (4 mg/day) (N = unclear*). 2. **Monotherapy:** clozapine (mean 500 mg/day SD 81.6) + placebo (N = unclear*). **Schedule:** not reported.
Outcomes	**- Usable data -** 1. Mental state: PANSS.
Notes	*N randomised not reported. Conference proceeding.

Risk of bias

Bias	Authors' judgement	Support for judgement

C +haloperidol 2006 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"Randomised" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"10 patients gave informed consent to participation, while 6 patients completed the study". N randomised to each group not reported.
Selective reporting (reporting bias)	High risk	Not all expected outcomes reported.
Other bias	Unclear risk	Source of funding not reported.

C +haloperidol 2010

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 6 weeks. **Setting:** inpatient. **Design:** parallel. **Country:** Taiwan.
Participants	**Diagnosis:** schizophrenia (DSM-IV). **N** = 88. **Sex:** M 51, F 37. **Age:** average 38 years. **History:** newly hospitalised schizophrenic patients with acute exacerbation.
Interventions	1. **Combination therapy:** 2 mg/d risperidone + 2 mg/day haloperidol (N = 46). 2. **Monotherapy:** 4 mg/day risperidone (N = 42). **Schedule:** not reported.
Outcomes	**- Usable data -** 1. Leaving the study early. 2. Clinical response: not clinically improved (< 30% reduction in total PANSS scores), CGI-S, GAF. 3. Mental state: PANSS. 4. Adverse events: Serious adverse events, weight gain, movement disorders. 5. Economic burden: cost of care. **- Unable to use -** 1. Quality of life: SF-36 (No total scores reported). 2. Adverse events: AIMS, BAS, SAS, prolactin (Skewed data). **- Not used in review -** 1. CDSS (Calgary Depression Scale for Schizophrenia) time to clinical response; time to discontinuation; BMI, pulse rate, blood pressure, fasting glucose, liver function, renal function, lipid profiles.

C +haloperidol 2010 *(Continued)*

Notes	Clinical Trials.gov identifier: NCT00998608.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, no further details.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blind, no further details.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Efficacy analysis was carried out with the LOCF method for participants that did not stay in the study at week 6. Analyses of safety assessments were conducted on all randomised patients (N = 88).
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported.
Other bias	Low risk	Funded by the Kai-Suan Psychiatry Hospital, the National Science Council (Taiwan), National Health Research Institutes (Taiwan), Department of Health (Taiwan), Department of Health Clinical Trial and Research Center of Excellence, and China Medial University Hospital (Taiwan).

C +levomepromazine 2004

Methods	**Allocation:** randomised. **Blinding:** open-label. **Duration:** 8 weeks. **Setting:** inpatients. **Design:** parallel. **Country:** Japan.
Participants	**Diagnosis:** schizophrenia (DSM-IV). **N** = 19. **Sex:** M 12, F 7. **Age:** average ~ 29 years. **History:** not medicated before this trial..
Interventions	1. **Combination therapy:** haloperidol + levomepromazine (N = 9). 2. **Monotherapy:** haloperidol (N = 10). **Schedule:** Dose adjustment was made on the basis of clinical response and tolerance, except that the dose ratio was fixed at 1:10 for the combined therapy.
Outcomes	**- Usable data -** 1. Leaving the study early. 2. Mental state: BPRS. **- Not used in review -**

C +levomepromazine 2004 *(Continued)*

1. ECGs, blood pressure or heart rate.

Notes	*Data were extrapolated from figures.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label trial.
Incomplete outcome data (attrition bias) All outcomes	High risk	Four patients were taken off the monotherapy, because of little improvement in their agitation. There were no dropouts in the combined group.
Selective reporting (reporting bias)	High risk	Not all expected outcomes reported.
Other bias	Unclear risk	Funding not reported.

C +olan/risp 2014

Methods	**Allocation:** randomised. **Blinding:** single-blind. **Duration:** 12 weeks. (10 weeks randomised). **Setting:** inpatient. **Design:** parallel. **Country:** Japan, multi-centre.
Participants	**Diagnosis:** schizophrenia, schizophreniform disorder, or schizoaffective disorder (DSM-IV-TR). **N** = 51*. **Sex:** M 22, F 29. **Age:** ~ 45. **History:** acute/non responders. Most patients were behavioral emergencies and about 60% were brought in by the police. Only early non responders (CGI-I score ≥ 4) were randomised after a 2 week trial with either risperidone or olanzapine.
Interventions	1. **Combination therapy:** olanzapine (Mean = 19.0 mg) augmented with risperidone (Max = 8.1 mg/day) (N = 11). 2. **Combination therapy:** risperidone (Mean = 8.7 mg/day) augmented with olanzapine (Max. dose 16.1 mg/day) (N = 14). 3. **Monotherapy:** olanzapine (Max = 18.8) (N = 13). 4. **Monotherapy:** risperidone (Max = 8.2) (N = 11).
Outcomes	**- Usable data -** 1. Clinical Response: not clinically improved, CGI-I and GAF

C +olan/risp 2014 *(Continued)*

	2. Leaving the study early. 3. Mental state: PANSS (Total, Positive, Negative). 4. Adverse event: requiring discontinuation, any movement disorder, weight gain. **- Not able to use -** 1. Adverse event: prolactin levels (Skewed data). **- Not used in this review -** 1. Five factor model of the PANSS, triglycerides, LDL, fasting glucose and BMI.
Notes	*51/156 participants were early non-responders to risperidone or olanzapine and were randomised to the two intervention groups. Clinical register: UMIN000007145.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"For randomization, we referred to a random number table".
Allocation concealment (selection bias)	Low risk	"Sequentially numbered, opaque, sealed envelopes used to conceal the allocation sequence."
Blinding (performance bias and detection bias) All outcomes	High risk	Rater-blinded. Participants where not blinded to the intervention.
Incomplete outcome data (attrition bias) All outcomes	High risk	Almost 50% (25/51) of participants did not completed the study.
Selective reporting (reporting bias)	Low risk	The study protocol was published but is not available. The published report include all expected outcomes, including those that were pre-specified.
Other bias	Unclear risk	Funded by the Ministry of Health, Welfare, and Labor of the Japanese Government and Intramural Research Grant for Neurological and Psychiatric Disorders.

C +olanzapine 2012

Methods	**Allocation:** randomised. **Blinding:** rater blinded. **Duration:** 10 weeks. **Setting:** inpatient. **Design:** parallel. **Country:** Japan.
Participants	**Diagnosis:** schizophrenia, schizophreniform disorder, or schizoaffective disorder (DSM IV-TR). **N** = 26*. **Sex:** M 13, F 13. **Age:** average 39.5 years. **History:** newly admitted patients with acute schizophrenia who were early non-responders to risperidone.

C +olanzapine 2012 *(Continued)*

Interventions	1. **Combination therapy:** risperidone (< 6 mg/day) + Olanzapine (< 20 mg/day) (N = 13). 2. **Monotherapy:** risperidone, starting at 3 mg/day, at 2 weeks < 6 mg/day was allowed and at 8 weeks < 12 mg/day (N = 13).
Outcomes	**- Usable data -** 1. Leaving the study early. 2. Clinical response: not clinically improved (< 50% improvement in PANSS total), CGI-I, GAF. 3. Mental state: PANSS. 4. Adverse events: serious event or requiring discontinuation, movement disorders, average weight gain. **- Not used in review -** Time to treatment discontinuation, blood levels change from baseline (mg/dL); fasting glucose, cholesterol, triglycerides.
Notes	*26/78 participants were early non-responders to risperidone and were randomised to the two intervention groups. UMIN Clinical Trials Registry: UMIN000003531.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, no further details.
Allocation concealment (selection bias)	Low risk	Opaque, sealed envelopes "We referred to a random number table, with sequentially numbered, opaque, sealed envelopes used to conceal the allocation sequence".
Blinding (performance bias and detection bias) All outcomes	High risk	Participants and personnel were not blinded. Blind outcome assessment "Rater blinded".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Although 13 participants discontinued treatment, ITT analysis was carried out of all 26 participants.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported.
Other bias	Low risk	Supported by grants from the Ministry of Health, Welfare, and Labor of the Japanese Government.

C +olanzapine 2012b

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 24 weeks (12 weeks for each phase*). **Setting:** inpatients. **Design:** cross-over. **Country:** Finland.

C +olanzapine 2012b *(Continued)*

Participants	**Diagnosis:** schizophrenia. **N** = 14. **Sex:** M 11, F1 (data from participants who ended the study). **Age:** ~ 48 years. **History:** Treatment resistant schizophrenic participants with a GAF score < 25 who were currently on therapy with clozapine-olanzapine combination.
Interventions	1. **Combination therapy:** clozapine + olanzapine (N = 7). 2. **Monotherapy:** clozapine + placebo (N = 7).
Outcomes	**- Usable data -** 1. Leaving the study early. **- Not able to use -** 1. Clinical response: CGI-S and GAF (Unable to extract the data from table 2, as it is unclear which results belong which group).
Notes	* The first 4 weeks of the study were used for tapering the group from clozapine + olanzapine to monotherapy with clozapine.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	”Randomized” No other information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind: “Olanzapine and placebo were dispensed in similar gelatin capsules that were formulated for this trial.” “The rater was blind to the study medication (i.e., either olanzapine or placebo) until the completion of the trial in each case.”
Incomplete outcome data (attrition bias) All outcomes	High risk	Imbalance in the number of missing data, as one group lost 4 (57%) patients while the other had no losses.
Selective reporting (reporting bias)	High risk	Unable to use data for GAF and CGI as the results are presented without specifying the group to which they correspond.
Other bias	Low risk	The study was supported by funding from the Annual EVO Financing (special government subsidies from the Ministry of Health and Welfare, Finland).

C +perphenazine 1976

Methods	**Allocation:** randomised. **Blinding**: double-blind. **Duration:** 8 weeks. **Setting:** inpatients. **Design:** parallel. **Country:** Japan, multi-centre.
Participants	**Diagnosis:** schizophrenia.

C +perphenazine 1976 *(Continued)*

	N = 317. **Sex:** M 196, F 155. **Age:** range 26-31 years. **History:** chronic.
Interventions	1. **Combination therapy:** carpipramine + chlorpromazine (N = 118) 2. **Combination therapy:** perphenazine + chlorpromazine (N = 116) 3. **Monotherapy:** chlorpromazine + placebo (N = 107) **Schedule:** chlorpromazine 75 mg to 200 mg/day (fixed), carpipramine and perphenazine not reported.
Outcomes	**- Usable data -** 1. Leaving the study early. 2. Clinical response: not clinically improved, relapse. 3. Adverse events: serious or requiring discontinuation, movement disorders, death. **- Unable to use -** 1. Keio Univ Psychiatric Symptom Scale, Keio Univ Behaviour Rating Scale (Not reported).
Notes	*Abstract in English, report in Japanese.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned, no further information.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical tablets were used for active drugs and placebo.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided.
Selective reporting (reporting bias)	High risk	Not all expected outcomes reported.
Other bias	Unclear risk	No source of funding reported.

C +pimozide 2011

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 12 weeks. **Setting:** inpatient. **Design:** parallel. **Country:** USA.
Participants	**Diagnosis:** schizophrenia, schizoaffective disorder (DSM-IV).

C +pimozide 2011 *(Continued)*

	N = 53. **Age:** average 32 years. **History:** stable dose of clozapine demonstrated to have been associated with a clozapine plasma level greater than 378 Cg/mL for at least eight weeks and partially or completely unresponsive to clozapine monotherapy.
Interventions	1. **Combination therapy:** clozapine (mean 518.8 SD 117.3) + pimozide (mean 6.48 mg/day, SD 2.18, max 8 mg) (N = 25). 2. **Monotherapy:** clozapine (mean 478.1 mg/day, SD 150.2) + placebo (N = 28).
Outcomes	**- Usable data -** 1. Leaving the study early. 2. Clinical response: CGI-S. 3. Mental state: PANSS. 4. Adverse events: serious or requiring discontinuation. **- Unable to use -** 1. Specific Level of Function scale (SLOF) (no overall scores reported). 2. Extrapyramidal Symptom Rating Scale (ESRS) (no overall scores reported). **- Not used in review -** 1. Blood pressure, pulse, ECG.
Notes	ClinicalTrials.gov identifier NCT00158223.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, no further details.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blind, "Given that the increased risk of extrapyramidal symptoms associated with pimozide threatened the integrity of the blind, assignment of assessments ensured that the rating of the ESRS was carried out by personnel different from those performing the PANSS and functional competence ratings."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Although 12% of combined group participants and 18% of placebo group participants discontinued treatment, all participants randomised were included in the analyses.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported.
Other bias	Low risk	Source of funding NIMH.

C +pimozide 2013

Methods	**Allocation:** randomised. **Blinding:** double-blind.

C +pimozide 2013 *(Continued)*

	Duration: 12 weeks. **Setting:** outpatients. **Design:** parallel. **Country:** USA, multi-centre.
Participants	**Diagnosis:** schizophrenia and schizoaffective disorder (DSM-IV). **N** = 32*. **Age:** ~ 42.9. **History:** currently taking clozapine with blood level of at least 350 ng/ml and on stable dose of clozapine for past 2 weeks.
Interventions	1. **Combination therapy:** clozapine (Mean blood levels: 650 ng/mL) + pimozide (Max dose 4 mg) (N = 14). 2. **Monotherapy:** clozapine (Mean blood levels 519 ng/dL) + placebo (N = 14).
Outcomes	**- Usable data -** 1. Leaving the study early. 2. Adverse event: requiring discontinuation. 3. Mental state: BPRS. **- Unable to use -** 1. Clinical Response: CGI-S and CGI-I (Skewed data). 2. Mental state: SANS (Skewed data). 3. Adverse events: SAS, AIMS (Not reported). 4. Service utilisation: hospital admission (Unable to impute). **- Not used in this review -** 1. Neurocognitive measures: Controlled Word Association Test, Digit Symbol Coding, Rey Auditory Verbal Learning Test, Digit Span and Letter-Number Sequencing and Trail Making Test.
Notes	*Only reported outcomes for 28 patients as 4 patients withdrew prior to receiving medication. ClinicalTrials.gov Identifier: NCT00374244.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized". No other information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: "Patients were randomized to identical looking pimozide or placebo capsules by the research pharmacist who was not involved with the subjects."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for missing outcome data unlikely to be related to true outcome.
Selective reporting (reporting bias)	High risk	Adverse events reported as: "no significant medication effects for AIMS, SAS, systolic or diastolic blood pressure, heart rate, weight or QTc values over time."
Other bias	High risk	Imbalance of clozapine blood levels: "subjects in the augmentation arm showing significantly higher clozapine levels".

C +pimozide 2013 *(Continued)*

	From protocol: Expected sample size was not met.

C +pipotiazine 2000

Methods	**Allocation:** randomised (no further information). **Blinding:** not stated. **Duration:** 3 months. **Setting:** unclear if community or inpatient. **Design:** parallel. **Country:** China.
Participants	**Diagnosis:** schizophrenia (CCMD-2-R). **N** = 50. **Age:** average age 25±9 years. **Sex:** male and female. **Average length of illness:** 6 ± 4 years.
Interventions	1. **Combination therapy:** pipotiazine (25 mg administered though muscle injection at the start of the trial, a further 50 mg was administered two weeks later. After that, 50 mg to 100 mg/month until the end of trial) + clozapine (491.62 mg ± 30.68 mg) (N = 26). 2. **Monotherapy:** clozapine (489.81 mg ± 29.73 mg/day) (N = 24).
Outcomes	**- Usable data -** 1. Clinical response: not clinically improved. 2. Mental state: BPRS, SANS*. **- Unable to use -** 1. Adverse events: movement disorders (TESS)* (Skewed data). **- Not used in review -** 1. ECG.
Notes	*N not reported, assumed to be the same as for the outcome 'not clinically improved'.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, but no further information.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome data.

C +pipotiazine 2000 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	All measured outcomes were reported. N not reported for BPRS, SANS and TESS.
Other bias	Low risk	None obvious.

C +risperidone 2001

Methods	**Allocation:** randomised (no further information). **Blinding:** not stated. **Duration:** 8 weeks. **Setting:** inpatients. **Design:** parallel. **Country:** China.
Participants	**Diagnosis:** schizophrenia (CCMD-2). **N** = 326. **Age:** clozapine group 40.2 ± 8.7 years, risperidone group 38.9 ± 9.4 years, combination group 39.4 ± 9.2 years. **Sex:** male and female. **Average length of illness:** clozapine group 9.1 ± 4.2 years, risperidone group 8.6 ± 3.4 years, combination group 8.9 ± 3.7 years.
Interventions	1. **Combination therapy:** clozapine (150 mg ± 72 mg/day) + risperidone (1.5 mg ± 1.3 mg/day) (N = 109). 2. **Monotherapy:** clozapine (375 mg ± 112 mg/day) (N = 106). 3. **Monotherapy:** risperidone (4.3 mg ± 1.2 mg/day) (N = 111).
Outcomes	**- Usable data -** 1. Clinical response: not clinically improved*. 2. Mental state: PANSS*. 3. Adverse events: drowsiness, white cell count*.
Notes	*N not reported, assumed to be same as the number randomised.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, no further information.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome data.

C +risperidone 2001 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	All measured outcomes were reported. N not reported for outcomes.
Other bias	Low risk	None obvious.

C +risperidone 2001b

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 8 weeks. **Setting:** inpatients. **Design:** parallel. **Country:** China.
Participants	**Diagnosis:** schizophrenia. **N** = 101. **Sex:** M and F (numbers not reported). **Age:** 16-58 years, average ~ 25 years. **History:** refractory, chronic.
Interventions	1. **Combination therapy:** clozapine (200 mg) + risperidone (6 mg) (N = 32). 2. **Monotherapy:** clozapine (≤ 600 mg) (N = 34). 3. **Monotherapy:** risperidone (≤ 8 mg) (N = 35). **Schedule:** daily dose.
Outcomes	**- Usable data -** 1. Clinical response: not clinically improved. 2. Adverse events: movement disorders. 3. Leaving the study early. **- Unable to use -** 1. PANSS, CGI and TESS (not reported).
Notes	*Abstract in English, report in Chinese.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly divided into 3 groups (while claiming to be randomised - participants were matched on the type and stage of illness).
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All included patients completed the trial.

C +risperidone 2001b *(Continued)*

Selective reporting (reporting bias)	High risk	PANSS, CGI and TESS scores were measured, but not reported.
Other bias	Unclear risk	Source of funding not reported.

C +risperidone 2001c

Methods	**Allocation:** randomised (no further information on randomisation method used). **Blinding:** not stated. **Duration:** 12 weeks. **Setting:** inpatients. **Design:** parallel. **Country:** China.
Participants	**Diagnosis:** schizophrenia (CCMD-2-R). **N** = 96. **Age:** 18-60 years. **Sex:** male and female. **History:** average length of illness, mean ˜ 4.5 years, SD ˜ 3.5 years.
Interventions	1. **Combination therapy:** clozapine (average ˜ 100 mg/day) + risperidone (1 mg to 4 mg/day) (N = 32). 2. **Monotherapy:** clozapine (50 mg to 400 mg/day) (N = 32). 3. **Monotherapy:** risperidone (1 mg to 6 mg/day) (N = 32).
Outcomes	**- Usable data -** 1. Clinical response: not clinically improved. 2. Mental state: BPRS*.
Notes	*N not reported, assumed to be the same as for the outcome 'not clinically improved'.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, no further information.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome data.
Selective reporting (reporting bias)	Unclear risk	All measured outcomes were reported. N not reported for BPRS.
Other bias	Low risk	None obvious

C +risperidone 2005

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 6 weeks. **Setting:** 6 inpatients and 24 outpatients. **Design:** parallel. **Country:** Turkey.
Participants	**Diagnosis:** schizophrenia (DSM-IV). **N** = 30. **Sex:** M 20, F 10. **Age:** average ~ 33 years. **History:** received clozapine treatment (300 mg to 900 mg/day) for at least 6 months, had previously failed to respond adequately, i.e. had persistent positive symptoms, to at least 2 trials of adequate duration and dose of antipsychotic drugs other than clozapine.
Interventions	1. **Combination therapy:** clozapine (600 mg to 900 mg/day) + risperidone (2 mg to 6 mg/day) (N = 16). 2. **Monotherapy:** clozapine (600 mg to 900 mg/day) + placebo (N = 14)*.
Outcomes	**- Usable data -** 1. Leaving the study early. 2. Clinical response: not clinically improved. 3. Mental state: no clinical improvement, PANSS. 4. Quality of life: QLS. 5. Adverse events: serious or requiring discontinuation, weight gain, extrapyramidal, change in prolactin level, SAS. **-Unable to use -** 1. Clinical response: CGI-S, GAF (Skewed data). 2. Adverse events: AIMS, BAS, UKU (Skewed data); white blood count (Not reported). **- Not used in review -** 1. Calgary Depression Scale (CDS).
Notes	*Initially received 1 identical pill administered after the evening meal, increased to 2 after first week and then to 3 (1 after breakfast, 2 after evening meal) after second week.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation planned by unblinded investigators, a pre-assigned random sequence was determined for each site.
Allocation concealment (selection bias)	Low risk	Pre-assigned random sequence in order with their enrolment.
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical pills containing either risperidone or placebo were added to clozapine.
Incomplete outcome data (attrition bias) All outcomes	High risk	One patient from combination group did not complete the study. No further information given.

C +risperidone 2005 *(Continued)*

Selective reporting (reporting bias)	High risk	Not all expected outcomes reported.
Other bias	High risk	Not all patients suggested from sample size calculation were recruited. Protocol not available and Janssen Pharmaceuticals.

C +risperidone 2005b

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 12 weeks. **Setting:** inpatients and outpatients. **Design:** parallel **Country:** USA.
Participants	**Diagnosis:** schizophrenia or schizoaffective disorder (DSM-IV). **N** = 40. **Sex:** M 35, F 5. **Age:** average ~ 40 years. **History:** before treatment with clozapine, documented treatment failure after two antipsychotics approved by the U.S. Food and Drug Administration were administered for an adequate duration in a sufficient dose (6 or more weeks of 1000 mg/day of chlorpromazine equivalents); demonstrated a documented failure to show a satisfactory clinical response to an adequate trial of clozapine (3 or more months of at least 600 mg/day of oral clozapine or a plasma drug level of 350 ng/mL or higher); and had persistent psychotic symptoms.
Interventions	1. **Combination therapy:** clozapine + risperidone (N = 20). 2. **Monotherapy:** clozapine + placebo (N = 20). **Schedule:** risperidone 1 mg to 6 mg/day, clozapine baseline doses established by treating psychiatrists and remained stable throughout the study.
Outcomes	**- Usable data -** 1. Leaving the study early. 2. Clinical response: not clinically improved. 3. Mental state: SANS, BPRS. 4. Adverse events: movement disorders. **- Unable to use -** 1. Adverse events: SAS (no SDs reported, no suitable mean to impute data); white cell counts (Not reported).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were randomly assigned in a 1:1 ratio to augmentation with risperidone or matching placebo.
Allocation concealment (selection bias)	Low risk	Each patient's study medication dose was managed by a non-blinded research fellow not involved in any aspect of patient care who acted as intermediary between the study investigators, treating psychiatrist, and pharmacy.

C +risperidone 2005b *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	The raters, treating psychiatrist, and patient remained blinded throughout the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All included patients completed the trial.
Selective reporting (reporting bias)	High risk	Not all expected outcomes reported.
Other bias	High risk	This study was funded by Johnson & Johnson Pharmaceutical Research & Development.

C +risperidone 2006

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 8 weeks. **Setting:** inpatients and outpatients. **Design:** parallel. **Country:** Canada, Germany, China, and the UK.
Participants	**Diagnosis:** schizophrenia or schizoaffective disorder (DSM-IV). **N** = 68. **Sex:** M 50, F 18. **Age:** average ~ 35 years. **History:** treatment with clozapine for the indication of poor response to other antipsychotic agents; treatment for at least 12 weeks at a stable dose of 400 mg or more per day, unless the size of the dose was limited by side effects.
Interventions	1. **Combination therapy:** clozapine + risperidone (N = 34). 2. **Monotherapy:** clozapine + placebo (N = 34). **Schedule:** risperidone 1 mg to 3 mg tablets/day, clozapine average 490 mg/day.
Outcomes	**- Usable data -** 1. Leaving the study early. 2. Clinical response: not clinically improved, CGI-S. 3. Mental state: PANSS. 4. Adverse events: serious or requiring discontinuation, weight gain, ESRS, drowsiness, white cell counts. **- Unable to use -** 1. Clinical response: CGI-I (Not reported). 2. Adverse events: BAS (Skewed data). **- Not used in review -** 1. Brown–Peterson procedure, Letter-Number Sequencing (LNS) task, fasting blood glucose, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides.
Notes	*After the double-blinded phase, the patients were offered the option of receiving unblinded augmentation of clozapine treatment with risperidone for an additional 18 weeks.

C +risperidone 2006 *(Continued)*

Protocol: ClinicalTrials.gov number NCT00272584.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed according to a computer-generated schedule with a permuted-block design. The fixed block size was four patients.
Allocation concealment (selection bias)	Low risk	The site investigators did not know the block size. The person generating the randomisation schedule was not involved in determining the patients' eligibility, administering treatment, or determining outcome. The patients were assigned in sequence at each site.
Blinding (performance bias and detection bias) All outcomes	Low risk	Throughout the study, the patients, sight investigators, and raters remained blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Primary analysis was performed according to the ITT principle.
Selective reporting (reporting bias)	High risk	Not all stated outcomes reported.
Other bias	Unclear risk	Supported by a grant from the Stanley Medical Research Institute. Risperidone and placebo were provided by Janssen, Canada.

C +risperidone 2007

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 6 weeks. **Setting:** outpatients. **Design:** parallel. **Country:** USA.
Participants	**Diagnosis:** refractory schizophrenia (DSM-IV). **N** = 24. **Sex:** 21 M, 3 F. **Age:** average 42.3 years (range 27-55). **History:** displayed stable, residual psychiatric symptoms; failed at least two previous trials of antipsychotics prior to clozapine and currently treated with clozapine monotherapy for at least 6 months, at a stable dose for at least 8 weeks and with clozapine plasma levels of at 200 ng/mL, unless the clozapine dose necessary to achieve that level was not tolerated.
Interventions	1. **Combination therapy:** clozapine + risperidone (N = 11). 2. **Monotherapy:** clozapine + placebo (N = 13). **Schedule:** risperidone 4 mg/day, clozapine 456 mg/day average (200 mg to 700 mg/day). Subjects received one capsule twice daily for three days, then two capsules twice daily for the rest of the study.
Outcomes	**- Usable data -** 1. Leaving the study early. 2. Clinical response: not clinically improved.

C +risperidone 2007 *(Continued)*

	3. Mental state: PANSS, SANS. **- Unable to use -** 1. Adverse events: AIMS, SAS, BAS (Skewed data); prolactin level (no SD reported, not able to impute as no similar mean); Systematic Assessment for Treatment Emergent Events (SAFTEE; no data reported). **- Not used in review -** 1. Calgary Depression Scale for Schizophrenia (CDSS).
Notes	*The active 6-week treatment period was preceded by a 2-week single-blind placebo lead-in period to eliminate potential placebo-responders. ClinicalTrials.gov identifier NCT00289861.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants randomised in blocks of 10. No further details.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding (performance bias and detection bias) All outcomes	Low risk	An independent research pharmacy prepared matching capsules that contained either 1 mg risperidone or placebo.
Incomplete outcome data (attrition bias) All outcomes	High risk	Twopatients in the placebo group and three patients in the risperidone group did not finish the study.
Selective reporting (reporting bias)	High risk	Not all expected outcomes reported.
Other bias	Unclear risk	Trial supported by a grant from the Stanley Medical Research Institute.

C +sertindole 2006

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 12 weeks. **Setting:** unclear. **Design:** parallel. **Country:** Denmark.
Participants	**Dignosis:** schizophrenia (ICD10, F20.0-3). **N** = 50. **Sex:** M 30, F 20. **Age:** average 42 years. **History:** clozapine treatment minimum 6 months, total PANSS > 65, no antipsychotic other than clozapine drug 1 month prior.
Interventions	1. **Combination therapy:** clozapine + sertindole 16 mg/day (N = 25).

C +sertindole 2006 *(Continued)*

	2. **Monotherapy:** clozapine + placebo (N = 25).
Outcomes	**- Usable data -** 1. Leaving the study early. 2. Service use: hospital admission. 3. Clinical response: GAF. 4. Mental state: PANSS. 5. Adverse events: serious or requiring discontinuation, death, weight gain, average weight gain, drowsiness, tremor. **- Unable to use -** 1. Clinical response: CGI-S (reported as 0 mean change (CI 0 to 0) for both treatment groups). 2. Clinical response: CGI-I (reported as 0 mean change (CI -1 to 0) for both treatment groups). 3. Quality of life: World Health Organization Quality of Life Brief Questionnaire (QoL-BREF) (no overall scores reported).. 4. Adverse events: UKU side effects rating scale (no overall scores reported). **- Not used in review -** 1. Cogntive tests, Drug Attitude Inventory, fasting glucose, lipids, Hb1Ac.
Notes	ClinicalTrials.gov identifier NCT00345982.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation.
Allocation concealment (selection bias)	Low risk	Central allocation, "Randomization […] was administered by the local pharmacy that had no affiliation to the study".
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants, personnel and assessors were blinded, "Blinding was concealed until the end of the 12-week visit, and disclosure of the blinding was first done after reporting all PANSS values to the pharmacy to ensure that the primary outcome data could not be changed after unblinding". Blinded raters performed all clinical research assessments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All analyses were performed as completers analyses and ITT analyses, using the LOCF principle.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported.
Other bias	High risk	H. Lundbeck supported the study with a study grant and study medication. They had no influence on conduct of the study or preparation of the manuscript.

C +sulpiride 1997

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 10 weeks.

C +sulpiride 1997 *(Continued)*

	Setting: not reported. **Design:** parallel. **Country:** Israel.
Participants	**Diagnosis:** schizophrenia (DSM-IV). **N** = 28. **Sex:** M 19, F 9. **Age:** average ˜ 39 years. **History:** failed to respond to at least three types of typical antipsychotics; partial and unsatisfactory response to clozapine following at least 12 weeks of treatment in an adequate dose.
Interventions	1. **Combination therapy:** clozapine + sulpiride (N = 16). 2. **Monotherapy:** clozapine + placebo (N = 12). **Schedule:** sulpiride was raised to 600 mg/day by 100 mg/day increments and thereafter remained constant for the rest of the study period. Clozapine dosage (range 400 mg to 450 mg/day) remained unchanged for the entire study.
Outcomes	**- Usable data -** 1. Leaving the study early. 2. Cinical response: not clinically improved. 3. Mental state: BPRS, SAPS, SANS. 4. Adverse events: serious or requiring discontinuation, change in prolactin level. **- Unable to use -** 1. Adverse events: white blood cell counts (Not reported). **- Not used in review -** 1. Hamilton Rating Scale for Depression (HAM-D).
Notes	*The sulpiride or placebo was added for 10 consecutive weeks. All assigned participants finished the study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly allocated according to a table of random numbers.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding (performance bias and detection bias) All outcomes	Low risk	The placebo tablets were made to appear identical to the sulpiride tablets by the manufacturer.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All included patients completed the trial.
Selective reporting (reporting bias)	High risk	Not all expected outcomes reported.
Other bias	Unclear risk	Funding not reported.

C +sulpiride 1999

Methods	**Allocation:** 'randomised' according to clinic admission order. **Blinding:** not stated. **Duration:** 12 weeks. **Setting:** community patients. **Design:** parallel. **Country:** China.
Participants	**Diagnosis:** schizophrenia (CCMD-2-R). **N** = 150. **Sex**: male and female. **Age**: mean ˜ 26 years, SD ˜ 7.78 years. **History:** length of illness: mean ˜ 2.4 years, SD ˜ 1.3 years..
Interventions	1. **Combination therapy:** sulpiride (1390.2 mg ± 104.86 mg/day) + clozapine (25 mg to 75 mg/day) (N = 50). 2. **Monotherapy:** clozapine (486.17 mg ± 30.8 mg/day) (N = 50). 3. **Monotherapy:** sulpiride (1390.2 mg ± 104.86 mg/day) (N = 50).
Outcomes	**- Usable data -** 1. Clinical response: not clinically improved. 2. Mental state: BPRS. 3. Adverse events: white blood cell counts. **- Unable to use -** 1. Adverse events: TESS (Skewed data).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomised, according to clinic attendance sequence.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome data.
Selective reporting (reporting bias)	Low risk	All measured outcomes were reported.
Other bias	Low risk	None obvious.

C +sulpiride 1999b

Methods	**Allocation:** randomised according to hospital admission order. **Blinding:** double-blind **Duration:** 6 weeks. **Setting:** inpatients **Design:** parallel **Country:** China
Participants	**Diagnosis:** schizophrenia (CCMD-2-R) **N** = 41. **Age:** 21-49 years. **Sex:** female only. **History:** length of illness 3 months to 20 years, BPRS score greater than or equal to 38.
Interventions	1. **Combination therapy:** clozapine (350 mg/day), sulpiride (800 mg/day) (N = 20). 2. **Monotherapy:** clozapine (350 mg/day) (N = 21).
Outcomes	**- Usable data -** 1. Clinical response: not clinically improved. 2. Mental state: BPRS, SANS. 3. Adverse events: movement disorders, drowsiness. **- Unable to use -** 1. Adverse events: TESS (Not reported).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomised, according to hospital admission order.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome data.
Selective reporting (reporting bias)	High risk	TESS was measured, but not reported.
Other bias	Low risk	None obvious.

C +sulpiride 1999c

Methods	**Allocation:** randomised. **Blinding:** double-blind. **Duration:** 12 weeks. **Setting:** inpatients. **Design:** parallel. **Country:** China.
Participants	**Diagnosis:** schizophrenia (mainly exhibiting negative symptoms). **N** = 88. **Sex:** M and F (Not reported). **Age:** average ~ 35 years.
Interventions	1. **Combination therapy:** clozapine 50 mg to 500 mg + chlorimipramine 50 mg to 150 mg (N = 29). 2. **Combination therapy:** clozapine (50 mg to 500 mg) + sulpiride (0.2 mg to 1.0 mg) (N = 29). 3. **Monotherapy:** clozapine (50mg to 500 mg) (N = 30). **Schedule:** daily dose.
Outcomes	**- Usable data -** 1. Leaving the study early. 2. Clinical response: not clinically improved. 3. Mental state: BPRS. **- Unable to use -** 1. Mental state: SANS (Skewed data). 2. Adverse events: TESS (Skewed data).
Notes	*Abstract in English, report in Chinese.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, but randomisation method was not described.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All included patients completed the trial.
Selective reporting (reporting bias)	High risk	Not all expected outcomes reported.
Other bias	Unclear risk	Source of funding not reported.

C +sulpiride 2003

Methods	**Allocation:** randomised ('randomised' is only mentioned in abstract, not mentioned at all in the full text). **Blinding:** not stated. **Duration:** 3 months. **Setting:** inpatients. **Design:** parallel. **Country:** China.
Participants	**Diagnosis:** schizophrenia (CCMD-2-R). **N** = 98. **Age:** average age ˜ 32 years. **Sex:** male and female. **History:** chronic treatment resistant. Length of illness: average ˜ 7 years (range 2-29 years).
Interventions	1. **Combination therapy:** clozapine + sulpiride; dosages are the monotherapy arms (N = 30). 2. **Monotherapy:** clozapine (150 mg ˜ 300 mg/day) (N = 31). 3. **Monotherapy:** sulpiride (300 mg ˜ 600 mg/day) (N = 29).
Outcomes	**- Usable data -** 1. Clinical response: not clinically improved. 2. Mental state: BPRS, SANS. 3. Adverse events: movement disorders. **- Unable to use -** 1. Mental state: SAPS (no SD, not able to impute data as no similar means).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, no further information.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 cases were excluded from final analysis as they did not complete the 3-month treatment. 4 cases dropped out due to allergy to clozapine, 1 case dropped out due to allergy to sulpiride.
Selective reporting (reporting bias)	Low risk	All measured outcomes were reported.
Other bias	Low risk	None obvious.

C +sulpiride 2004

Methods	**Allocation:** randomised. **Blinding:** no. **Duration:** 8 weeks. **Setting:** outpatients ("day patients"). **Design:** parallel. **Country:** Israel.
Participants	**Diagnosis:** schizophrenia (DSM-IV). **N** = 17. **Sex:** M 9, F 8. **Age:** average ~ 31 years. **History:** chronic. Illnesses longer than 2 years duration.
Interventions	1. **Combination therapy:** olanzapine + sulpiride (N = 9). 2. **Monotherapy:** olanzapine (N = 8). **Schedule:** sulpiride 100 mg to 600 mg/day, olanzapine 20 mg to 30 mg/day.
Outcomes	**- Usable data -** 1. Leaving the study early. 2. Mental state: PANSS. **- Unable to use -** 1. Adverse events: SAS, BAS (Skewed data). **- Not used in review -** 1. Hamilton Scale for Depression (HAM-D) and the Hamilton Scale for Anxiety (HAM-A).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding (performance bias and detection bias) All outcomes	High risk	Limitations for the study include the absence of a double-blind, placebo-controlled study design, and non-blind rating.
Incomplete outcome data (attrition bias) All outcomes	High risk	Only those 16 patients who completed the study were included in the final statistical analysis.
Selective reporting (reporting bias)	High risk	Not all expected outcomes reported.
Other bias	Unclear risk	This study was not supported by any funding. No protocol- a priori was published.

C +sulpiride 2006

Methods	**Allocation:** randomised (as stated in the abstract only, there is no description in the full text at all). **Blinding:** not stated. **Duration:** 8 weeks. **Setting:** unclear if it's inpatients or community. **Design:** parallel. **Country:** China.
Participants	**Diagnosis:** schizophrenia (CCMD-III). **N** = 64. **Age:** 16-60 years. **Sex:** male and female. **History:** length of illness: 8.48 ± 5.42 years in combination group; 8.79 ± 6.73 years in clozapine group.
Interventions	1. **Combination therapy:** clozapine (25 mg, twice a day) + sulpride (200-600 mg/d) (N = 32). 2. **Monotherapy:** clozapine: 25 mg, twice a day (N = 32).
Outcomes	**- Usable data -** 1. Clinical response: not clinically improved. 2. Mental state: SANS. 3. Adverse events: weight gain.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, no further information.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is unclear if there are incomplete outcome data.
Selective reporting (reporting bias)	Low risk	All measured outcomes were reported.
Other bias	Low risk	None obvious.

C +sulpiride 2013

Methods	**Allocation:** randomised. **Blinding:** double-blind.

C +sulpiride 2013 *(Continued)*

	Duration: 6 weeks. **Setting:** inpatient. **Design:** parallel. **Country:** Taiwan.
Participants	**Diagnosis:** schizophrenia (DSM IV). **N** = 96*. **Sex:** M 54, F 38. **Age:** 38.6 ± 9.0. **History:** Hospitalised schizophrenic patients with acute exacerbation, had a baseline Clinical Global Impression-Severity of Illness Scale (CGI- S) of at least 4. After a washout period of at least 3 days, patients were assigned randomly to either treatment for 6 weeks.
Interventions	1. **Combination therapy:** combination of low-dose amisulpride (400 mg/day) plus low-dose sulpiride (800 mg/day). Drugs were administered orally in two divided doses (N = 49). 2. **Monotherapy:** full-dose amisulpride (800 mg/day). Drugs were administered orally in two divided doses (N = 47).
Outcomes	**- Usable data -** 1. Clinical Response: not clinically improved, CGI-S, GAF. 2. Leaving the study early. 3. Mental State: PANSS (Total, Positive, Negative). 4. Adverse events: serious event, AIMS, BAS, SAS, tremor, prolactin levels, weight gain (Binary and average kg). 5. Economic burden: drug cost. 6. Quality of life: Short Form-36 (mental component summary and physical component summary). **- Unable to use -** Adverse events: prolactin levels (Skewed data). **- Not used in this review -** 1. Metabolic parameters, CDSS.
Notes	* 92 patients are included in the ITT analysis. Unpublished data were provided by the investigator. ClinicalTrials.gov identifier NCT01615185.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	From correspondence: Randomisation was made by creating a list with software.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	“Double blind”. No other information provided.

C +sulpiride 2013 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	"Study completion rates were similar in the two groups: 31 (67.4%) of 46 patients in the antipsychotic combination group and 32 (69.6%) of 46 patients in the monotherapy group-"
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported. Protocol available.
Other bias	Unclear risk	Funded by the Kai-Syuan Psychiatric Hospital in 2011, the Food and Drug Administration, Department of Health, Taiwan, the National Science Council, Taiwan, China Medical University Hospital, Taiwan and the Taiwan Department of Health Clinical Trial and Research Center of Excellence.

AIMS - Abnormal Involuntary Movement Scale.
ASEX - Arizona Sexual Experience Scale.
BACS - Brief Assessment of Cognition in Schizophrenia.
BAS - Barnes Akathisia Scale.
BMI – Body Mass Index.
BPRS - Brief Psychiatric Rating Scale.
CCMD - Chinese Classification of Mental Disorders.
CDSS - Calgary Depression Scale for Schizophrenia.
CGI-I - Clinical Global Impression - Improvement.
CGI-S - Clinical Global Impression - Severity.
CI - confidence interval.
DAI - Drug Attitude Inventory.
DIEPSS - Drug-Induced Extrapyramidal Symptoms Scale.
DSM-IV - Diagnostic and Statistical Manual of Mental Disorders.
ECG - Electrocardiogram.
ECT- Electroconvulsive therapy.
ESRS - Extrapyramidal Symptom Rating Scale.
ESS - Epworth Sleepiness Scale.
FSI - Fatigue Symptom Inventory.
GAF - Global Assessment of Functioning Scale.
GEOPTE - Scale of social cognition for psychosis.
HAM-A - Hamilton Scale for Anxiety.
HAM-D - Hamilton Rating Scale for Depression.
HDL - high density lipoprotein.
HVA - plasma homovanillic acid.
IAQ - Investigator Assessment Questionnaire.
ICD - International Classification of Diseases.
IM - intramuscular.
ITT - intention-to-treat.
LOCF - last-observation-carried forward.
LDL - low-density lipoprotein.
MADRS - Montgomery–Åsberg Depression Rating Scale.
NIMH - National Institute of Mental Health.
NOSIE - Nurses Observation Scale for Inpatient Evaluation.
PANSS - Positive and Negative Syndrome Scale.
QLS - Quality of Life Scale.
QoL-BREF- Quality of Life Brief Questionnaire.
SAFTEE - Systematic Assessment for Treatment Emergent Events.
SAI -Schedule for Assessment of Insight.
SANS - Scale for the Assessment of Negative Symptoms.
SAPS - Scale for the Assessment of Positive Symptoms.
SAS - Simpson Angus Scale.
SD - standard deviation.
SF-36 - Short Form health survey.
SG - glucose effectiveness.
SI - insulin sensitivity index.
SLOF - Specific Level of Function scale.

SMP- Slow moving proteinase a common gastric aid.
SWN - Subjective Well Being under Neuroleptics.
TESS - Treatment Emergent Symptom Scale
UKU - Udvalg for Kliniske Undersøgelser.
VLDL - very low-density lipoprotein.
WCST - Wisconsin Card Sorting Test.
YBOCS - Yale-Brown Obsessive Compulsive Scale.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ahn 2002	**Allocation:** randomised. **Participants**: adult patients with schizophrenia. **Interventions**: direct switching method vs start-tapering switching method.
Alptekin 2012	**Allocation:** randomised. **Participants:** adults with DSM-IV diagnosis of schizophrenia. **Interventions:** slowly increasing the dose of sertindole with immediate discontinuation of the current antipsychotic after randomisation vs slowly increasing the dose of sertindole with decreasing the dose of the current antipsychotic. **Outcomes:** Drop out, PANSS, EPS, metabolic parameters and Qtc prolongation.
Awad 2014	**Allocation:** randomised. **Participants:** adults with clinically stable DSM-IV defined schizophrenia or schizoaffective disorder. **Interventions:** lurasidone vs different doses of lurasidone.
Barbui 2011	**Allocation:** randomised. **Participants:** people with schizophrenia. **Interventions:** combination treatment clozapine plus aripiprazole vs combination treatment clozapine plus haloperidol.
Cazorla 2012	**Allocation:** randomised. **Participants:** adults with DSM-IV diagnosis of schizophrenia. **Interventions:** switching to asenapine vs switching to olanzapine. **Outcomes:** stability, PANSS, discontinuation, BMI and adverse events.
ChiCTR-TRC-14004854	**Allocation:** randomised. **Participants:** adults with schizophrenia. **Interventions:** paliperidone extended-release tablets vs olanzapine.
Citrome 2012	**Allocation:** randomised. **Participants:** outpatients with a DSM IV-TR diagnosis of schizophrenia. **Interventions:** switch immediately to iloperidone or to gradually taper their prior antipsychotic dose over the first 2 weeks of iloperidone use.
Dai 2012	**Allocation:** randomised. **Participants:** adults with schizophrenia and hyperlipidaemia. **Interventions:** antipsychotic medication and synthetical intervention vs antipsychotic medication.
Dai 2012a	**Allocation:** randomised. **Participants:** schizophrenia.

Study	Reason for exclusion
	Interventions: group therapy and risperidone vs risperidone.
DRKS00008018	**Allocation:** randomised. **Participants:** patients with a first episode of schizophrenia according to DSM-V. **Interventions:** treatment with any antipsychotic drug for at least 12 months vs treatment with any antipsychotic drug only for first episode of schizophrenia, tapering-off medication after remission of positive symptoms. **Outcomes:** Total grey matter volume, assessment of safety, drop out rates, PANSS, BACS, SF-36.
Fang 2012	**Allocation:** randomised. **Participants:** people with schizophrenia. **Interventions:** risperidone and clonazepam (a benzodiazepine, not an antipsychotic) vs haloperidol.
Fleischhacker 2012	**Allocation:** randomised. **Participants:** subjects with schizophrenia requiring chronic treatment with an antipsychotic. **Interventions:** aripiprazole (400 mg/month) vs aripiprazole (50 mg/month) versus oral aripiprazole (10 mg to 30 mg/day). **Outcomes:** time to relapse and adverse events.
Fleischhacker 2013	**Allocation:** randomised. **Participants:** adults with DSM-IV diagnosis of schizophrenia. **Interventions:** aripiprazole once monthly IM depot vs placebo once monthly IM depot. **Outcomes:** Leaving the study early, SAS, BAS.
Goff 2008	**Allocation:** randomised. **Participants:** people with schizophrenia. **Interventions:** antipsychotic (clozapine, olanzapine or risperidone) plus add on therapy CX516 (AMPA-receptor-positive modulator, potential treatment for cognitive deficits in schizophrenia) vs antipsychotic plus placebo.
Henderson 2009	**Allocation:** randomised, cross-over. **Participants:** people with schizophrenia. **Interventions:** olanzapine plus aripiprazole vs olanzapine plus placebo. **Outcomes:** PANSS, SANS, HDRS, GAF, Fatigue Scale Inventory, Quality of Life Scale, SAS, BAS, AIMS, and anthropomorphic, blood pressure and metabolic assessments. **No usable data:** results not given for each phase of the trial separately.
Hwang 2015	**Allocation:** randomised. **Participants:** diagnosis of schizophrenia or schizoaffective disorder according to the DSM IV. **Interventions:** fast tapering off the current medication within 1 week after initiating aripiprazole vs slow tapering off the current medication within 4 weeks after initiating aripiprazole.
JPRN-UMIN000011710	The trial could not start and ended before patients were enrolled.
JPRN-UMIN000012729	**Allocation:** randomised. **Participants:** schizophrenia. **Interventions:** blonaserin (atypical antipsychotic) vs aripiprazole. **Outcomes:** PANSS, DAI-10, CGI.
JPRN-UMIN000017047	**Allocation:** randomised. **Participants:** adults with DSM-IV diagnosis of schizophrenia. **Interventions:** blonanserin as add-on therapy vs olanzapine as add-on therapy.

Study	Reason for exclusion
	Outcome: change in total score of the PANSS between baseline and endpoint (12 months).
Kelly 2005	**Allocation:** randomised. **Participants:** people with schizophrenia. **Interventions:** divalproex extended release (DV-ER) and lithium vs DV-ER and quetiapine versus DV-ER and placebo.
Kreinin 2006	**Allocation:** not randomised. **Participants:** people with schizophrenia. **Outcomes:** nocturnal hypersalivation rating scale, PANSS, CGI, SAS, plasma prolactin levels. **No usable data:** results not given for each phase of the trial separately.
Kwon 2012	**Allocation:** randomised. **Participants:** adults with DSM-IV diagnosis of schizophrenia. **Interventions:** sertindole vs olanzapine. **Outcomes:** leaving the study early, PANSS, CGI, adverse events.
Lerner 2004	**Allocation:** not randomised.
Li 2013	**Allocation:** randomised. **Participants:** adults with schizophrenia. **Interventions:** liqi xingshen decoction vs risperidone.
Lieberman 2009	**Allocation:** randomised. **Participants:** people with schizophrenia. **Interventions:** antipsychotic (quetiapine or risperidone) plus TC-5619 (partial agonist at the α7 subtype of the neural nicotinic acetylcholine receptors, potential treatment for cognitive dysfunction in schizophrenia) vs antipsychotic plus placebo.
Lieberman 2013	**Allocation:** randomised. **Participants:** patients aged 18–60 years DSM-IV-TR defined schizophrenia. **Interventions:** cariprazine vs aripiprazole vs placebo. **Outcomes:** Leaving the study early, PANSS, CGI-S.
Lundbeck 2004	**Allocation:** randomised. **Participants:** adults with DSM-IV diagnosis of schizophrenia. **Interventions:** bifeprunox (30 mg or 40 mg once daily) vs risperidone (4 mg or 6 mg once daily).
Lundbeck 2008	**Allocation:** randomised. **Participants:** people with schizophrenia. **Interventions:** risperidone and Lu AE58054 (selective 5-HT6 antagonist, potential treatment for cognitive deficits in schizophrenia) vs risperidone and placebo.
Mantovani 2013	**Allocation:** randomised. **Participants:** patients who presented with an acute agitation state requiring medication for rapid tranquillization. **Interventions:** haloperidol and promethazine vs haloperidol and midazolam versus olanzapine vs ziprasidone.
Meltzer 2008	**Allocation:** randomised. **Participants:** adults with diagnosis of acute schizophrenia.

Study	Reason for exclusion
	Intervention: paliperidone (6 mg, 9 mg, and 12 mg/day) vs olanzapine (10 mg daily) vs placebo.
Meltzer 2012	**Allocation:** randomised. **Participants:** patients who met DSM-IV criteria for schizophrenia, with a recent acute exacerbation of psychotic symptoms. **Intervention:** risperidone and pimavanserin (inverse agonist of the 5-HT2A receptor) vs haloperidol and pimavanserin vs risperidone and placebo vs haloperidol and placebo.
Mi 2013	**Allocation:** randomised. **Participants:** schizophrenia. **Interventions:** antipsychotic medication plus psychotherapy vs antipsychotic medication.
Mir 2008	**Allocation:** not randomised.
Mythri 2013	**Allocation:** randomised. **Participants:** acute agitation in patients with psychiatric disorders.
NCT01003379	**Allocation:** randomised. **Participants:** people with schizophrenia. **Interventions:** antipsychotic (quetiapine or risperidone) and TC-5619 (partial agonist at the α7 subtype of the neural nicotinic acetylcholine receptors, potential treatment for cognitive dysfunction in schizophrenia) vs antipsychotic and placebo.
NCT01234779	**Allocation:** randomised. **Participants:** people with schizophrenia. **Intervention:** bitopertin 10 mg/day or 30 mg/day (RO4917838 is glycine reuptake inhibitor) vs olanzapine 15 mg/day vs placebo.
NCT01939548	**Participants:** psychiatrically stable patients with schizophrenia who have had a suboptimal response to current treatment. **Interventions:** PF-02545920 (PDE10 inhibitor) vs placebo.
NCT02477670	**Participants:** patients who meet DSM IV-TR diagnostic criteria for schizophrenia. **Interventions:** AVP-786 (Deuterated [d6]-Dextromethorphan Hydrobromide [d6-DM]/Quinidine Sulfate, not an antipsychotic) vs placebo.
Pfizer 2009	**Allocation:** randomised. **Participants:** people with schizophrenia. **Interventions:** antipsychotic (risperidone, olanzapine, quetiapine, ziprasidone, paliperidone, or aripiprazole) and PF-03463275 (glycine transporter 1 (GlyT1) inhibitor vs antipsychotic (risperidone, olanzapine, quetiapine, ziprasidone, paliperidone, or aripiprazole) and placebo.
Ruiz-Doblado 2010	**Allocation:** narrative review.
Rupnow 2005	**Allocation:** randomised. **Participants:** people with schizophrenia. **Interventions:** in the 14-day monotherapy phase patients randomised to risperidone, quetiapine, or placebo, followed by 28-day additive-therapy phase during which clinicians allowed to add psychotropic medications.
Sacchetti 2006	**Allocation:** randomised. **Participants:** people with schizophrenia..

Study	Reason for exclusion
	Interventions: ziprasidone vs clozapine.
Semenikhin 2013	**Allocation:** randomised **Participants:** people with schizophrenia **Interventions:** cortexin vs placebo.
Sofronov 2013	**Allocation:** randomised. **Participants:** patients with paranoid schizophrenia according to the criteria of ICD 10. **Interventions:** sertindole monotherapy vs paliperidone monotherapy vs fluvoxamine in combination with zuclopenthixole.
Spyker 2015	**Allocation:** pharmacokinetics study. **Participants:** participants in this study were male and female patients between 18 and 65 years of age, who were on a stable, oral, chronic (more than 2 months) antipsychotic medication.
Stahl 2010b	**Allocation:** post-hoc extension evaluating monotherapy after combination treatment.
Sukegawa 2008	**Allocation:** randomised. **Participants:** adults with schizophrenia or related disorders. **Interventions:** reduction of antipsychotics using the method of RAS vs continuation of polypharmacy.
Sukegawa 2014	**Allocation:** randomised. **Participants:** were inpatients or outpatients diagnosed with schizophrenia according to the DSM-IV-TR. **Interventions:** safe correction of antipsychotic polypharmacy (SCAP) method versus the doses of antipsychotics were not changed for 3 months if clinically feasible.
UMIN000004931	**Allocation:** not randomised.
Wang 2013	**Allocation:** randomised. **Participants:** schizophrenia. **Interventions:** antipsychotic medication plus acupuncture vs antipsychotic medication.
Weiden 2013	**Allocation:** randomised. **Participants:** adults with schizophrenia or related disorders. **Interventions:** gradual-switch from risperidone to iloperidone vs immediate switch to open-label iloperidone. **Outcomes:** Integrated Clinical Global Impression of Change.
Wilson 1994	**Allocation:** not randomised; cohort study.
Winseck 2013	**Allocation:** randomised. **Participants:** adults with schizophrenia or related disorders. **Interventions:** gradual-switch from aripiprazole to iloperidone vs immediate switch to iloperidone. **Outcomes:** Integrated Clinical Global Impression of Change.
Wu 2002	**Allocation:** not randomised.
Wu 2015	**Allocation:** randomised. **Participants:** schizophrenia. **Interventions:** aripiprazole combined with ziprasidone and comprehensive and systematic nursing vs aripiprazole combined with ziprasidone and routine nursing.

Study	Reason for exclusion
Xia 2014	**Allocation:** randomised. **Participants:** adults with DSM-IV diagnosis of schizophrenia. **Interventions:** antipsychotics and wuji powder vs antipsychotics and aripiprazole.
Xu 2008	**Allocation:** randomised. **Participants:** people with schizophrenia. **Interventions:** sertraline plus sulpiride vs risperidone.
Yamanouchi 2015	**Allocation:** randomised. **Participants:** adults with schizophrenia (DSM IV). **Interventions:** safe correction of antipsychotic polypharmacy method vs stable dose of the current antipsychotics.
Yue 2004	**Allocation:** not randomised.
Zhang 2012	**Allocation**: quasi–randomised. **Participants**: adults with schizophrenia. **Interventions**: shugan-jieyu capsule and aripiprazole vs aripiprazole. **Outcomes**: clinical response, PANSS, adverse events.
Zhang 2013	**Allocation**: randomised. **Participants**: adults with schizophrenia. **Interventions**: venlafaxine with other antipsychotic vs antipsychotic medication. **Outcomes**: SANS, BPRS, TESS.
Zink 2009	**Allocation:** randomised. **Participants:** people with schizophrenia. **Interventions:** clozapine plus ziprasidone vs clozapine plus risperidone..

AIMS - Abnormal Involuntary Movement Scale
BACS - Brief Assessment of Cognition in Schizophrenia
BAS - Barnes Akathisia Scale
BMI – Body Mass Index
BPRS - Brief Psychiatric Rating Scale
CGI-S - Clinical Global Impression-Severity
DAI - Drug Attitude Inventory
DSM-IV - Diagnostic and Statistical Manual of Mental Disorders
EPS - extrapyramidal side effects
GAF - Global Assessment Scale of Functioning Scale
ICD - International Classification of Diseases
IM - intramuscular
PANSS - Positive and Negative Syndrome Scale
HDRS - Hamilton Depression Rating Scale
RAS - Reduction and Simplification
SANS - Scale for the Assessment of Negative Symptoms
SAS - Simpson Angus Scale
SF-36 - SF-form health survey
TESS - Treatment Emergent Symptom Scale

Characteristics of studies awaiting assessment *[ordered by study ID]*

NCT01450514

Methods	**Allocation:** randomised. **Blindness:** double-blind.
Participants	**Diagnosis:** schizophrenia or schizoaffective disorder. **N** = 40-60. **Age:** 18-65 years. **History:** patients treated during at least 12 weeks with a stable dosage of either risperidone depot of 12.5 mg to 50 mg IM every 2 weeks, paliperidone depot of 25 mg to 100mg IM every 4 weeks, risperidone oral administration of 2 mg to 6 mg/day, or paliperidone oral administration of 4 mg to 12 mg/day.
Interventions	1. **Combination therapy:** risperidone or paliperidone plus pipamperone (15 mg/day). 2. **Monotherapy:** risperidone or paliperidone plus placebo.
Outcomes	1. Functional MRI tests. 2. Positive and Negative Syndrome Scale (PANSS) items. 3. Subjective Well-being under Neuroleptics questionnaire (SWN) score. 4. Intrinsic Motivation Inventory for Schizophrenia Research (IMI-SR) questionnaire. 5. Clinical Global Impression if Improvement (CGI-I) score. 6. Barnes Akathisia Rating Scale (BARS) total and sub-item scores. 7. Brief Assessment of Cognition Scale (BACS) score and sub-item scores.
Notes	We contacted the principal investigator by e-mail to obtain data from this study, this clinical trial was carried out but the sponsor decided not to release the data as they wanted to keep them confidential. Sponsor: PharmaNeuroBoost N.V. ClinicalTrials.gov identifier: NCT01450514.

Xu 2006

Methods	**Allocation:** randomised. **Blindness:** single-blind.
Participants	**Diagnosis:** schizophrenia (CCMD-3). **N** = 60. **Age:** average 25 ± 6 years. **Sex:** Female.
Interventions	1. **Combination therapy:** risperidone or sulpiride plus aripiprazole 5 mg/day. 2. **Monotherapy:** risperidone or sulpiride plus placebo (vitamin C 100 mg/day).
Outcomes	1. Leaving the study early. 2. Mental state: BPRS. 3. Prolactin levels. 4. Adverse events.

Xu 2006 *(Continued)*

Notes	Vitamin C might have an effect on the symptoms of schizophrenia.

Yuan 2014

Methods	**Allocation:** randomised. **Blindness:** double-blind.
Participants	**Diagnosis:** first episode schizophrenia (DSM-IV).
Interventions	**Intervention:** 1. Stage 1: Risperidone (3 mg to 6 mg/day), aripiprazole (15 mg to 30 mg/day) or olanzapine (10 mg to 25 mg/day). 2. Stage 2: Change the current antipsychotic to one of the other two study drugs. 3. Stage 3: pharmacotherapy could be switched to any other atypical antipsychotic including long-acting medications. Furthermore, a combination with other antipsychotics or a certain adjunctive antidepressant was allowed for patients who still could not reach satisfactory outcome after the previous 2 stages. If the treatment failed as judged by the investigators and/or the patient, the patients entered the next stage of the trial.
Outcomes	1. Clinical response: CGI-S and CGI-I and < 50% reduction on the total score of the PANSS. 2. Mental state: PANSS. 3. Adverse events: UKU side-effect scale. 4. Treatment adherence: DAI. 5. Social functions: Personal and Social Performance scale. 6. Cognitive performance.
Notes	No response from responsible contact Xin Yu (yuxin@bjmu.edu.cn).

BACS - Brief Assessment of Cognition in Schizophrenia.
BAS - Barnes Akathisia Scale.
BPRS - Brief Psychiatric Rating Scale.
CCMD - Chinese Classification of Mental Disorders.
CGI-I - Clinical Global Impression - Improvement.
CGI-S - Clinical Global Impression - Severity.
DAI - Drug Attitude Inventory.
DSM - Diagnostic and Statistical Manual of Mental Disorders.
IM - intramuscular.
IMI-SR - Intrinsic Motivation Inventory for Schizophrenia Research.
MRI - magnetic resonance imaging.
PANSS - Positive and Negative Syndrome Scale.
SWN - Subjective Well Being under Neuroleptics.
UKU - Udvalg for Kliniske Undersøgelser.

Characteristics of ongoing studies *[ordered by study ID]*

CTRI-02-003397

Trial name or title	Randomised, double-blind, placebo-controlled trial to evaluate the effects of adjunctive treatment with aripiprazole on body weight, metabolic parameters, clinical efficacy, and adverse events in people with psychotic disorders on treatment with Clozapine.

CTRI-02-003397 *(Continued)*

Methods	**Allocation:** randomised. **Blindness:** double-blind. **Duration:** 16 weeks. **Country:** India.
Participants	**Diagnosis:** schizophrenia and schizoaffective (ICD-10). **Target sample size:** 60. **History:** Participants on a stable dose of clozapine (100 mg to 900 mg), with residual positive or negative psychotic or psychiatric symptoms with a minimum score on the Brief Psychiatric Rating Scale (BPRS) > 31, experiencing troublesome weight gain, and are overweight or obese. **Age:** 18 years or above.
Interventions	1. **Combination therapy:** clozapine + aripiprazole (10 mg to 20 mg/day). 2. **Monotherapy:** clozapine + placebo..
Outcomes	1. Clinical response: not clinical improved, and CGI (Efficacy index score). 2. Mental state: BPRS. 3. Adverse events: weight gain, SAS, sedation, hypersalivation. 4. Others: BMI, fasting sugars, triglycerides, lipids from baseline, compliance with diet, compliance with exercise.
Starting date	First enrolment on February 2013.
Contact information	Prince Rajamanickam (princer@cmcvellore.ac.in).
Notes	Clinical trial registry India ID: CTRI/2013/02/003397. Sponsor: Christian Medical College.

ISRCTN68824876

Trial name or title	Amisulpiride augmentation in clozapine-unresponsive schizophrenia.
Methods	**Allocation:** randomised. **Blindness:** double-blind. **Duration:** 12 months.
Participants	**Diagnosis:** schizophrenia. **Target sample size:** 230. **History:** persistent symptom severity despite adequate trial of clozapine, treatment for > 12 weeks (400 mg or more of clozapine/day), total score of 80 or greater on PANSS, CGI score of 4 or greater, SOFAS score of 40 or less. **Age:** 18-65 years.
Interventions	1. **Combination therapy:** amisulpiride + clozapine. 2. **Monotherapy:** placebo + clozapine.

ISRCTN68824876 *(Continued)*

Outcomes	1. Clinical response: not clinical improved (20% reduction in total PANSS score). 2. Mental state: PANSS negative symptom sub-scale score, CDSS. 3. Functioning: SOFAS. 4. Service use: Service engagement scale. 5. Adverse effects: Antipsychotic side effect measures. 6. Quality of life: Euroqol EQ-5D. 7. Economic: resource use data questionnaire.
Starting date	September 2010
Contact information	Prof. Thomas Barnes (t.r.barnes@imperial.ac.uk) Centre for Mental Health Imperial College Charing Cross Campus St Dunstan's Road London W6 8RP
Notes	ISRCTN trial registration ID: ISRCTN68824876 Sponsor: Imperial College London (UK)

Schmidt-Kraepelin 2013

Trial name or title	Is an antipsychotic combination treatment of olanzapine and amisulpiride more effective than monotherapy.
Methods	**Allocation:** randomised. **Blindness:** double-blind.
Participants	**Diagnosis:** schizophrenia or schizoaffective disorder. **Expected sample size:** 399. **Age:** 18-65 years. **History:** no details.
Interventions	1. **Combination therapy:** olanzapine and amisulpiride. 2. **Monotherapy:** olanzapine. 3. **Monotherapy:** amisulpiride.
Outcomes	1. Symptomatic improvement of schizophrenia in comparison to time of inclusion of patient measured by PANSS. 2. Serious adverse drug reactions. 3. Change of clinical condition measured by CGI scale. 4. Change of the subjective well-being measured by SWN scale.
Starting date	June 2012.
Contact information	Joachim Cordes (joachim.cordes@lvr.de). Sandra Feyerabend (sandra.feyerabend@lvr.de).

Schmidt-Kraepelin 2013 *(Continued)*

Notes	ClinicalTrials.gov identifier: NCT01609153. DRKS-ID: DRKS00003603. Sponsor: Heinrich-Heine University, Duesseldor.

BPRS - Brief Psychiatric Rating Scale
BMI - Body Mass Index
CGI - Clinical Global Impression
CDSS - Calgary Depression Scale for Schizophrenia
ICD - International Classification of Diseases
PANSS - Positive and Negative Syndrome Scale
SAS - Simpson Angus Scale
SOFAS - Social and Occupational Functioning Assessment Scale
SWN - Subjective Well Being under Neuroleptics

DATA AND ANALYSES

Comparison 1. ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical response: 1. No clinically important response - not improved	29	2398	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.64, 0.83]
1.1 clozapine in both groups	17	1127	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.53, 0.83]
1.2 other atypical in both groups	7	674	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.83, 1.09]
1.3 typical drugs in both groups	5	597	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.49, 0.84]
2 Clinical response: 2. Relapse	3	512	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.31, 1.29]
2.1 clozapine in both groups	1	70	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.54, 1.33]
2.2 typical drugs in both groups	2	442	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.16, 1.81]
3 Leaving the study early	43	3137	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.76, 1.07]
3.1 clozapine in both groups	18	932	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.88, 1.86]
3.2 other atypical drugs in both groups	15	1247	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.83, 1.27]
3.3 typical drugs in both groups	6	628	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.43, 1.12]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.4 any antipsychotics in both groups	4	330	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.30, 1.25]
4 Service utilisation: Hospital admission	3	202	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.36, 2.55]
4.1 clozapine in both groups	2	88	Risk Ratio (M-H, Random, 95% CI)	2.85 [0.31, 26.41]
4.2 any antipsychotics in both groups	1	114	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.25, 2.19]
5 Clinical response: 3. Global state - i. average severity score (CGI-S scale, high = bad)	7	496	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.31, 0.06]
5.1 clozapine in both groups	3	179	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.55, 0.47]
5.2 other atypical drugs in both groups	3	263	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.37, 0.05]
5.3 typical drugs in both groups	1	54	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.42, 0.22]
6 Clinical response: 3. Global state - ii. change in severity score (CGI-S scale, high = bad)	3	233	Mean Difference (IV, Random, 95% CI)	0.11 [-0.09, 0.32]
6.1 clozapine in both groups	1	53	Mean Difference (IV, Random, 95% CI)	0.21 [-0.09, 0.51]
6.2 other atypical drugs in both groups	2	180	Mean Difference (IV, Random, 95% CI)	0.03 [-0.24, 0.31]
7 Clinical response: 4. Global state - average improvement score (CGI-I scale, high = bad)	4	336	Mean Difference (IV, Random, 95% CI)	-0.36 [-0.58, -0.13]
7.1 clozapine in both groups	2	259	Mean Difference (IV, Random, 95% CI)	-0.33 [-0.56, -0.10]
7.2 other atypical drugs in both groups	2	77	Mean Difference (IV, Random, 95% CI)	-0.62 [-1.34, 0.10]
8 Clinical response: 5. Global state - i. average functioning score (GAF scale, high = good)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 Clozapine in both groups	1	30	Mean Difference (IV, Random, 95% CI)	-4.5 [-8.38, -0.62]
8.2 Other atypical drugs in both groups	2	77	Mean Difference (IV, Random, 95% CI)	8.73 [1.56, 15.90]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9 Clinical response: 5. Global state - ii. change in functioning score (GAF scale, high = good)	3	349	Mean Difference (IV, Random, 95% CI)	0.27 [-1.42, 1.97]
9.1 Clozapine in both groups	2	257	Mean Difference (IV, Random, 95% CI)	0.27 [-1.56, 2.10]
9.2 Other atypical drugs in both groups	1	92	Mean Difference (IV, Random, 95% CI)	0.30 [-4.21, 4.81]
10 Mental state: 1. Overall - a.i average total score (PANSS scale, high = bad)	11		Mean Difference (IV, Random, 95% CI)	Totals not selected
10.1 Clozapine in both groups	6		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
10.2 Other atypical drugs in both groups	4		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
10.3 Any antipsychotic in both groups	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
11 Mental state: 1. Overall - a.ii change in total score (PANSS scale, high = bad)	8	406	Mean Difference (IV, Random, 95% CI)	-1.05 [-3.42, 1.32]
11.1 Clozapine in both groups	3	133	Mean Difference (IV, Random, 95% CI)	-0.55 [-3.54, 2.43]
11.2 Other atypical drugs in both groups	5	273	Mean Difference (IV, Random, 95% CI)	-2.26 [-6.71, 2.18]
12 Mental state: 1. Overall - b.i. average total score (BPRS scale, high = bad)	21	1082	Mean Difference (IV, Random, 95% CI)	-4.15 [-6.17, -2.13]
12.1 clozapine in both groups	16	820	Mean Difference (IV, Random, 95% CI)	-5.19 [-7.08, -3.30]
12.2 other atypical drugs in both groups	2	68	Mean Difference (IV, Random, 95% CI)	-3.09 [-13.26, 7.08]
12.3 typical drugs in both groups	3	194	Mean Difference (IV, Random, 95% CI)	0.06 [-1.36, 1.48]
13 Mental state: 1. Overall - b.ii change total score (BPRS scale, high = bad)	1	100	Mean Difference (IV, Random, 95% CI)	-2.72 [-5.37, -0.07]
13.1 clozapine in both groups	1	100	Mean Difference (IV, Random, 95% CI)	-2.72 [-5.37, -0.07]
14 Mental state: 2. Specific - a. positive symptoms - no clinical improvement	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
14.1 clozapine in both groups	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15 Mental state: 2. Specific - b. positive symptoms - i. average score (PANSS scale, high = bad)	4	158	Mean Difference (IV, Random, 95% CI)	2.02 [0.90, 3.14]
15.1 clozapine in both groups	3	119	Mean Difference (IV, Random, 95% CI)	2.19 [0.92, 3.45]
15.2 any antipsychotics in both groups	1	39	Mean Difference (IV, Random, 95% CI)	1.40 [-1.03, 3.83]
16 Mental state: 2. Specific - b. positive symptoms - ii. change score (PANSS scale, high = bad)	9	891	Mean Difference (IV, Random, 95% CI)	0.01 [-0.45, 0.47]
16.1 clozapine in both groups	3	308	Mean Difference (IV, Random, 95% CI)	-0.39 [-1.08, 0.29]
16.2 other atypical drugs in both groups	6	583	Mean Difference (IV, Random, 95% CI)	0.33 [-0.28, 0.95]
17 Mental state: 2. Specific - b. positive symptoms - iii. average score (BPRS scale, high = bad)	3	133	Mean Difference (IV, Random, 95% CI)	-1.02 [-2.42, 0.38]
17.1 clozapine in both groups	2	93	Mean Difference (IV, Random, 95% CI)	-1.66 [-3.32, -0.00]
17.2 other atypical drugs in both groups	1	40	Mean Difference (IV, Random, 95% CI)	-0.07 [-1.61, 1.47]
18 Mental state: 2. Specific - b. positive symptoms - iv. change data (BPRS scale, high = bad)	1	17	Mean Difference (IV, Random, 95% CI)	-0.30 [-1.16, 0.56]
18.1 typical drugs in both groups	1	17	Mean Difference (IV, Random, 95% CI)	-0.30 [-1.16, 0.56]
19 Mental state: 2. Specific - b. positive symptoms - v. average score (SAPS scale, high = bad)	1	28	Mean Difference (IV, Random, 95% CI)	-6.76 [-11.91, -1.61]
19.1 other atypical drugs in both groups	1	28	Mean Difference (IV, Random, 95% CI)	-6.76 [-11.91, -1.61]
20 Mental state: 2. Specific - b. positive symptoms - vi. change score (SAPS scale, high = bad)	1	28	Mean Difference (IV, Random, 95% CI)	-5.80 [-11.33, -0.27]
20.1 clozapine in both groups	1	28	Mean Difference (IV, Random, 95% CI)	-5.80 [-11.33, -0.27]
21 Mental state: 3. Specific - a. negative symptoms - no clinical improvement	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21.1 clozapine in both groups	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
21.2 typical drugs in both groups	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
22 Mental state: 3. Specific - b. negative symptoms - i. average score (PANSS scale, high = bad)	5	194	Mean Difference (IV, Random, 95% CI)	1.16 [-0.49, 2.80]
22.1 clozapine in both groups	3	119	Mean Difference (IV, Random, 95% CI)	0.31 [-1.18, 1.80]
22.2 other atypical drugs in both groups	1	36	Mean Difference (IV, Random, 95% CI)	1.20 [-1.51, 3.91]
22.3 Any antipsychotic in both groups	1	39	Mean Difference (IV, Random, 95% CI)	3.30 [1.60, 5.00]
23 Mental state: 3. Specific - b. negative symptoms - ii. change score (PANSS scale, high = bad)	9	891	Mean Difference (IV, Random, 95% CI)	0.02 [-0.54, 0.58]
23.1 clozapine in both groups	3	308	Mean Difference (IV, Random, 95% CI)	0.31 [-1.11, 1.74]
23.2 other atypical drugs in both groups	6	583	Mean Difference (IV, Random, 95% CI)	0.01 [-0.69, 0.72]
24 Mental state: 3. Specific - b. negative symptoms - iii. average score (BPRS scale, high = bad)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
24.1 clozapine in both groups	1	61	Mean Difference (IV, Random, 95% CI)	-4.30 [-12.25, 3.65]
24.2 other atypical drugs in both groups	1	40	Mean Difference (IV, Random, 95% CI)	1.90 [0.69, 3.11]
25 Mental state: 3. Specific - b. negative symptoms - iv. change score (BPRS scale, high = bad)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
25.1 typical drugs in both groups	1	12	Mean Difference (IV, Random, 95% CI)	0.2 [-0.29, 0.69]
26 Mental state: 3. Specific - b. negative symptoms - v. average score (SANS scale, high = bad)	11		Mean Difference (IV, Random, 95% CI)	Totals not selected
26.1 clozapine in both groups	9		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
26.2 other atypical drugs in both groups	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
26.3 typical drugs in both groups	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
27 Mental state: 3. Specific - b. negative symptoms - vi. average score (SANS scale, high = bad)	1	28	Mean Difference (IV, Random, 95% CI)	-6.80 [-12.65, -0.95]
27.1 clozapine in both groups	1	28	Mean Difference (IV, Random, 95% CI)	-6.80 [-12.65, -0.95]
28 Mental state: 4. Specific - aggression/agitation - average score (BPRS scale, high = bad)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
28.1 typical drugs in both groups	1	12	Mean Difference (IV, Random, 95% CI)	-1.3 [-2.32, -0.28]
29 Adverse events: 1. General - a. serious event or requiring discontinuation	30	2398	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.65, 1.69]
29.1 clozapine in both groups	14	766	Risk Ratio (M-H, Random, 95% CI)	1.83 [0.82, 4.08]
29.2 other atypical in both groups	10	1016	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.37, 1.14]
29.3 typical drugs in both groups	3	403	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.09, 2.30]
29.4 any antipsychotics in both groups	3	213	Risk Ratio (M-H, Random, 95% CI)	2.84 [0.79, 10.29]
30 Adverse events: 1. General - b. death (suicide or non-suicide deaths)	4	897	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.13, 70.30]
30.1 clozapine in both groups	2	257	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.13, 70.30]
30.2 other atypical in both groups	1	323	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
30.3 typical drugs in both groups	1	317	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
31 Adverse events: 2. Movement disorders - a. any	20	1868	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.92, 1.25]
31.1 clozapine in both groups	8	545	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.69, 3.38]
31.2 other atypical in both groups	9	846	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.80, 1.18]
31.3 typical drugs in both groups	2	363	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.82, 2.05]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
31.4 any antipsychotics in both groups	1	114	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.60, 1.61]
32 Adverse events: 2. Movement disorders - b.i. average scores (SAS, high = bad)	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
32.1 clozapine in both groups	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
32.2 other atypical drugs in both groups	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
33 Adverse events: 2. Movement disorders - b.ii. change scores (SAS, high = bad)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
33.1 other atypical drugs in both groups	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
34 Adverse events: 2. Movement disorders - b.iii. average scores (TESS, high = bad)	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
34.1 clozapine in both groups	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
34.2 other atypical drugs in both groups	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
35 Adverse events: 2. Movement disorders - b.iv. average scores (DIEPSS, high = bad)	1	61	Mean Difference (IV, Random, 95% CI)	0.30 [-0.49, 1.09]
35.1 clozapine in both groups	1	61	Mean Difference (IV, Random, 95% CI)	0.30 [-0.49, 1.09]
36 Adverse events: 2. Movement disorders - b.v. change scores (BAS, high = bad)	2	91	Mean Difference (IV, Random, 95% CI)	-0.7 [-1.54, 0.14]
36.1 Other atypical drugs in both groups	2	91	Mean Difference (IV, Random, 95% CI)	-0.7 [-1.54, 0.14]
37 Adverse events: 2. Movement disorders - b.vi. change scores (AIMS, high = bad)	1	63	Mean Difference (IV, Random, 95% CI)	0.10 [-0.84, 1.04]
37.1 Other antipsychotic in both groups	1	63	Mean Difference (IV, Random, 95% CI)	0.10 [-0.84, 1.04]
38 Adverse events: 3. Endocrine - prolactin level (high = bad)	7		Mean Difference (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
38.1 clozapine in both groups	4		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
38.2 other atypical drugs in both groups	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
38.3 typical drugs in both groups	2		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
39 Adverse events: 4. Metabolic - a. weight gain (binary)	6	804	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.66, 1.53]
39.1 clozapine in both groups	4	389	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.34, 1.19]
39.2 other atypical in both groups	2	415	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.89, 1.99]
40 Adverse events: 4. Metabolic - b. average weight gain (kg)	9		Mean Difference (IV, Random, 95% CI)	Totals not selected
40.1 clozapine in both groups	6		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
40.2 other atypical drugs in both groups	3		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
41 Adverse events: 5. Blood - a. decreased white cell counts (binary)	2	315	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.04, 0.82]
41.1 clozapine in both groups	2	315	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.04, 0.82]
42 Adverse events: 5. Blood - b. average white cell counts ($10^{-3}/mm^3$)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
42.1 clozapine in both groups	1	61	Mean Difference (IV, Random, 95% CI)	0.66 [-0.20, 1.52]
43 Adverse events: 6. Central nervous system (CNS) - a. drowsiness	12		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
43.1 clozapine in both groups	6		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
43.2 other atypical in both groups	3		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
43.3 typical drugs in both groups	3		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
44 Adverse events: 6. Central nervous system (CNS) - b. tremor	4	222	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.47, 1.62]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
44.1 clozapine in both groups	3	130	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.12, 3.13]
44.2 Other atypical in both groups	1	92	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.47, 1.80]
45 Quality of life: 1a. Average score (QLS high=good)	1	30	Mean Difference (IV, Random, 95% CI)	0.80 [-5.44, 7.04]
45.1 clozapine in both groups	1	30	Mean Difference (IV, Random, 95% CI)	0.80 [-5.44, 7.04]
46 Quality of life: 1b. Average score (SWN, high=good)	2	248	Mean Difference (IV, Random, 95% CI)	2.05 [-1.08, 5.18]
46.1 clozapine in both groups	2	248	Mean Difference (IV, Random, 95% CI)	2.05 [-1.08, 5.18]
47 Quality of Life: 1c. Average score - Mental component summary (SF-36, high = good)	1	60	Mean Difference (IV, Random, 95% CI)	0.60 [-4.28, 5.48]
47.1 Other atypical in both groups	1	60	Mean Difference (IV, Random, 95% CI)	0.60 [-4.28, 5.48]
48 Quality of Life: 1d. Average score - Physical component summary (SF-36, high = good)	1	60	Mean Difference (IV, Random, 95% CI)	-1.70 [-4.71, 1.31]
48.1 Other atypical in both groups	1	60	Mean Difference (IV, Random, 95% CI)	-1.70 [-4.71, 1.31]
49 SUBGROUP ANALYSIS Clinical Response: Not clinically improved - Patients enrolled in the studies	18	1244	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.70, 0.93]
49.1 Chronic	14	987	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.63, 0.93]
49.2 Acute	4	257	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.73, 1.05]
50 SUBGROUP ANALYSIS Clinical Response: Not clinically improved - Treatment duration	28	2344	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.64, 0.83]
50.1 ≤12 weeks	21	1604	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.66, 0.89]
50.2 >12 weeks	7	740	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.51, 0.80]
51 SUBGROUP ANALYSIS Clinical Response: Not clinically improved - Use of clozapine in both groups	28	2344	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.64, 0.83]

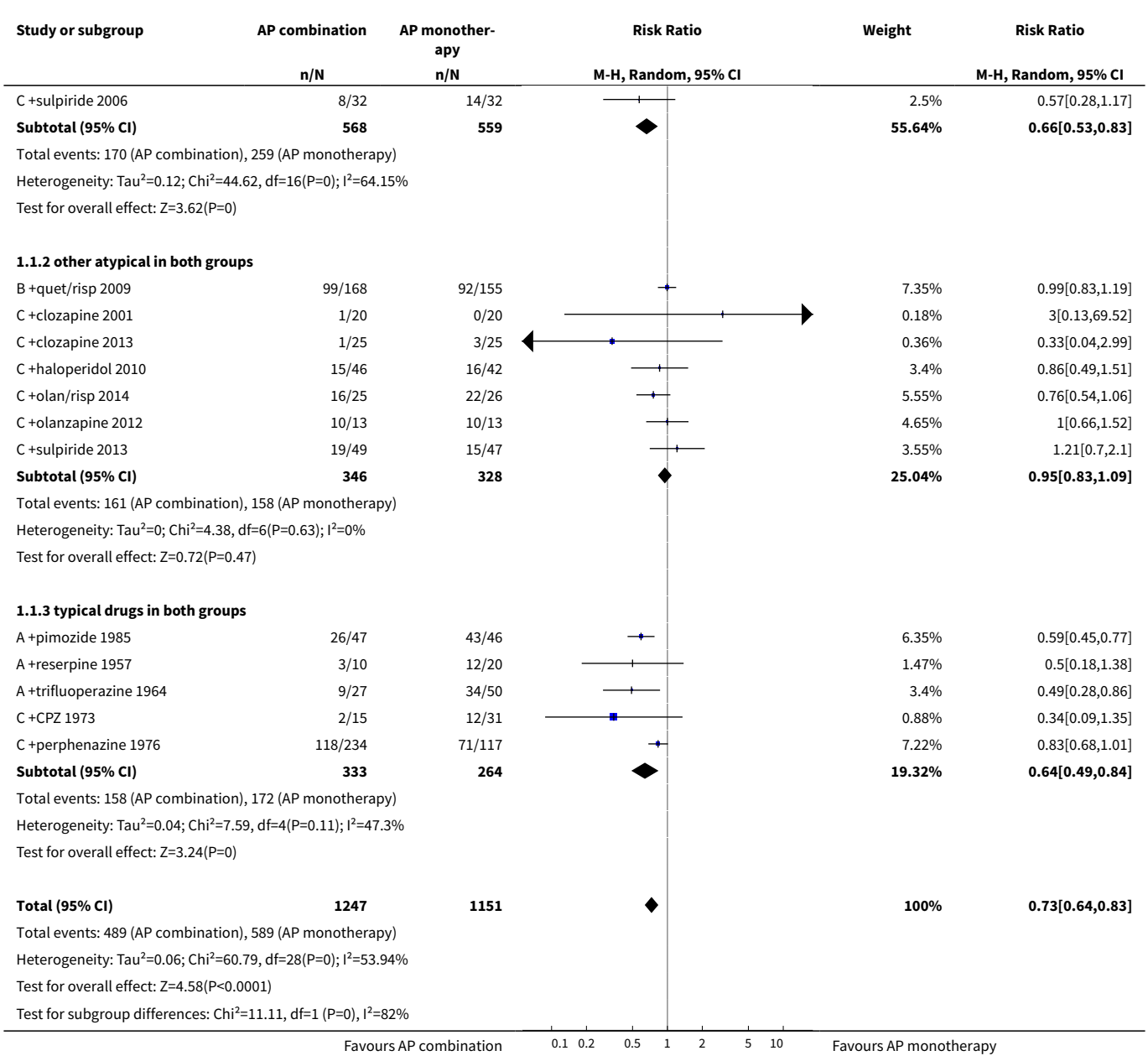
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
51.1 clozapine	17	1127	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.53, 0.83]
51.2 other antipsychotic	11	1217	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.69, 0.89]
52 SUBGROUP ANALYSIS Clinical Response: Not clinically improved - Drug added to clozapine	17	1127	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.53, 0.83]
52.1 Sulpirirde	8	486	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.43, 0.68]
52.2 Risperidone	7	507	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.68, 1.15]
52.3 Pipotazine	2	134	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.34, 0.74]
53 SUBGROUP ANALYSIS Leaving the study early - Patients enrolled in the studies	28	2208	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.74, 1.16]
53.1 Chronic	25	2075	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.69, 1.10]
53.2 Acute	3	133	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.53, 2.51]
54 SUBGROUP ANALYSIS Leaving the study early - Treatment duration	32	2454	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.77, 1.20]
54.1 ≤12 weeks	23	1426	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.78, 1.45]
54.2 >12 weeks	9	1028	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.66, 1.35]
55 SUBGROUP ANALYSIS Leaving the study early - Use of clozapine in both groups	32	2424	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.77, 1.20]
55.1 Clozapine	16	878	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.85, 1.86]
55.2 Other antipsychotics	16	1546	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.66, 1.20]
56 SUBGROUP ANALYSIS Leaving the study early - Drug added to clozapine	15	850	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.82, 1.82]
56.1 Risperidone	6	297	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.66, 2.67]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
56.2 Amisulpiride	1	16	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.06, 3.57]
56.3 Aripiprazole	4	347	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.78, 2.56]
56.4 Pimozide	1	53	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.18, 2.53]
56.5 Sertindole	1	50	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.38, 4.12]
56.6 Sulpiride	2	87	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
57 SENSITIVITY ANALYSIS Clinical Response: Not clinically improved - Randomisation	28	2344	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.64, 0.83]
57.1 Low / unclear risk of bias	25	2140	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.66, 0.85]
57.2 High	3	204	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.27, 0.71]
58 SENSITIVITY ANALYSIS Clinical Response: Not clinically improved - Double blind	28	2344	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.64, 0.83]
58.1 Low / unclear	25	2197	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.62, 0.82]
58.2 High	3	147	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.64, 1.01]
59 SENSITIVITY ANALYSIS Clinical response: 1. No clinically important response - not improved - Fixed effect	29	2398	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.68, 0.81]
59.1 clozapine in both groups	17	1127	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.56, 0.74]
59.2 other atypical in both groups	7	674	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.83, 1.11]
59.3 typical drugs in both groups	5	597	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.59, 0.81]
60 SENSITIVITY ANALYSIS Leaving the study early - Randomisation	30	2326	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.74, 1.18]
60.1 Low / unclear risk of bias	29	2298	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.74, 1.18]

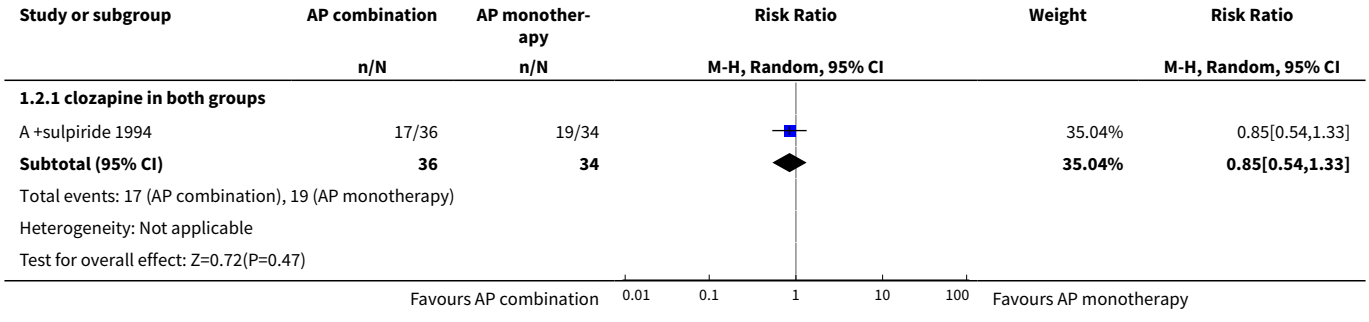
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
60.2 High risk	1	28	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
61 SENSITIVITY ANALYSIS Leaving the study early - Double blind	30	2326	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.74, 1.18]
61.1 Low / unclear risk	27	2156	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.74, 1.19]
61.2 High risk of bias	3	170	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.33, 2.82]
62 SENSITIVITY ANALYSIS Leving the study early - Fixed effect	43	3137	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.78, 1.04]
62.1 clozapine in both groups	18	932	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.92, 1.92]
62.2 other atypical drugs in both groups	15	1247	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.82, 1.25]
62.3 typical drugs in both groups	6	628	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.53, 0.92]
62.4 any antipsychotics in both groups	4	330	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.39, 0.84]

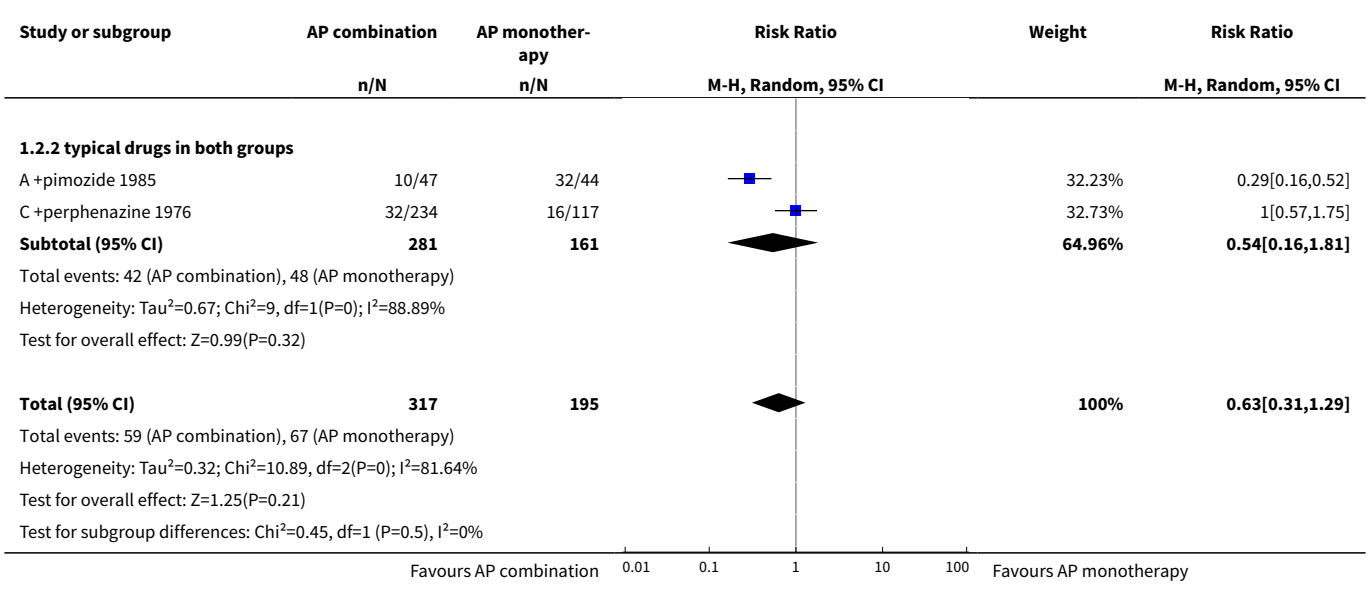
Analysis 1.1. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 1 Clinical response: 1. No clinically important response - not improved.

Study or subgroup	AP combination n/N	AP monotherapy n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 clozapine in both groups					
A +sulpiride 1994	15/36	21/34		4.2%	0.67[0.42,1.08]
B +pipotiazine 2002	16/42	31/42		4.6%	0.52[0.34,0.79]
B +sulpiride 1996	3/31	7/32		1.01%	0.44[0.13,1.56]
C +pipotiazine 2000	4/26	9/24		1.41%	0.41[0.15,1.16]
C +risperidone 2001	5/109	17/106		1.6%	0.29[0.11,0.75]
C +risperidone 2001b	13/34	12/32		3.05%	1.02[0.55,1.89]
C +risperidone 2001c	5/32	8/32		1.49%	0.63[0.23,1.71]
C +risperidone 2005	14/16	10/14		5.08%	1.23[0.84,1.79]
C +risperidone 2005b	13/20	18/20		5.36%	0.72[0.51,1.03]
C +risperidone 2006	28/34	25/34		6.51%	1.12[0.87,1.44]
C +risperidone 2007	9/11	12/13		5.74%	0.89[0.64,1.22]
C +sulpiride 1997	8/16	11/12		3.77%	0.55[0.32,0.92]
C +sulpiride 1999	12/50	28/50		3.52%	0.43[0.25,0.74]
C +sulpiride 1999b	2/20	4/21		0.67%	0.53[0.11,2.56]
C +sulpiride 1999c	4/29	11/30		1.44%	0.38[0.14,1.05]
C +sulpiride 2003	11/30	21/31		3.68%	0.54[0.32,0.92]
	Favours AP combination		0.1 0.2 0.5 1 2 5 10		Favours AP monotherapy

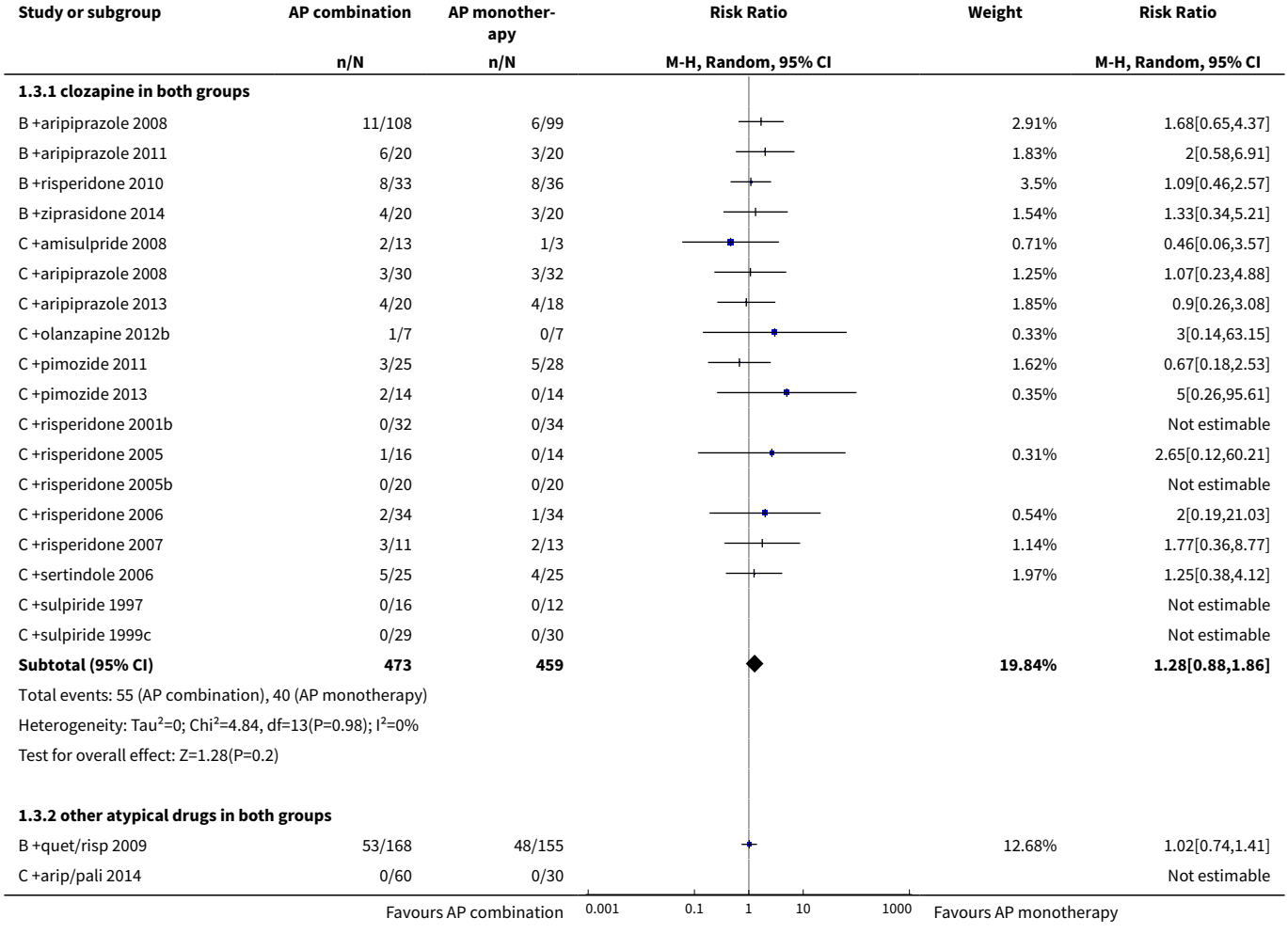


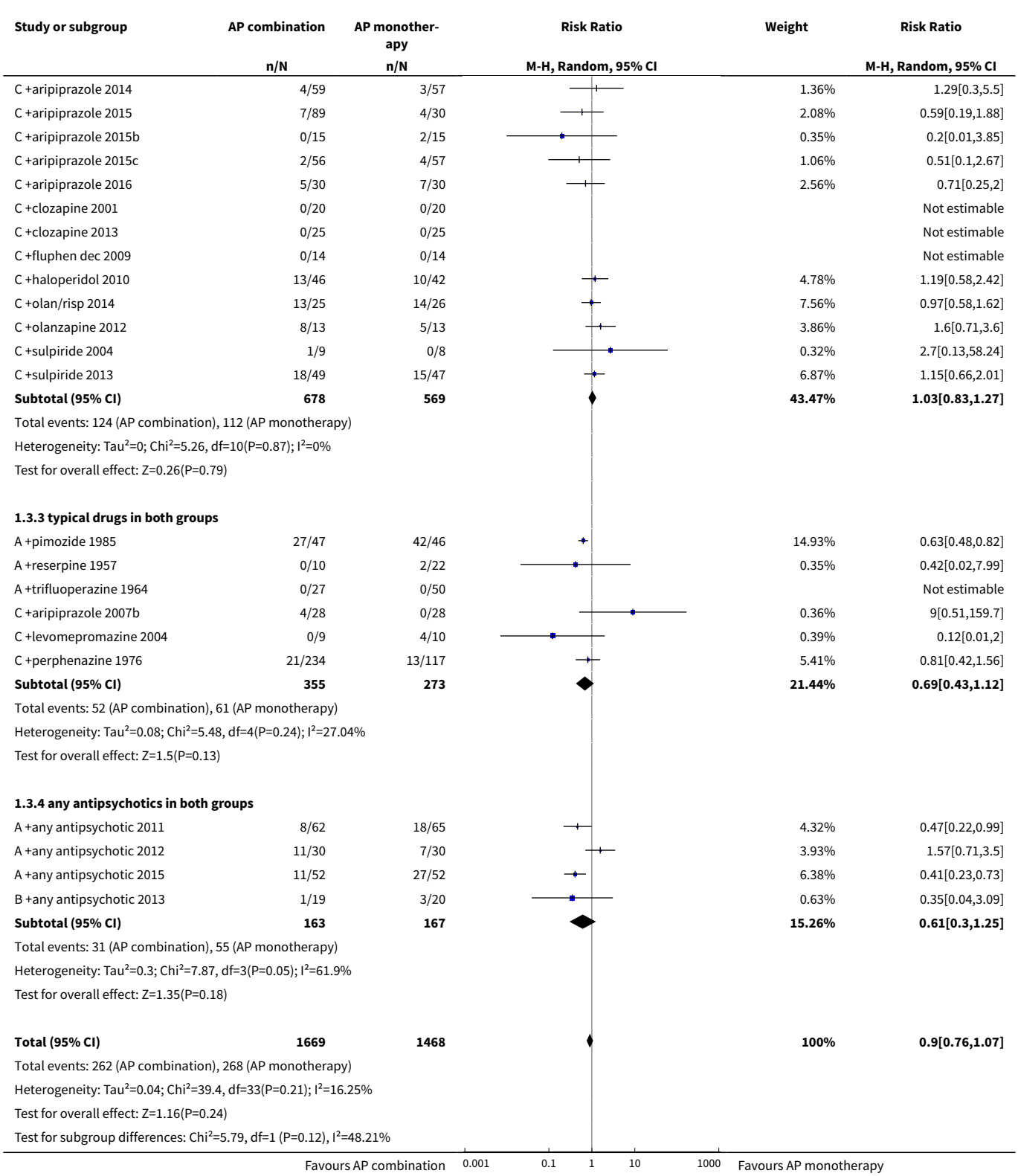
Analysis 1.2. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 2 Clinical response: 2. Relapse.





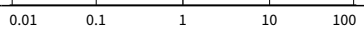
Analysis 1.3. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 3 Leaving the study early.





Analysis 1.4. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 4 Service utilisation: Hospital admission.

Study or subgroup	AP combination n/N	AP monotherapy n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 clozapine in both groups					
C +aripiprazole 2013	1/20	0/18		9.68%	2.71[0.12,62.7]
C +sertindole 2006	1/25	0/25		9.59%	3[0.13,70.3]
Subtotal (95% CI)	**45**	**43**		**19.27%**	**2.85[0.31,26.41]**
Total events: 2 (AP combination), 0 (AP monotherapy)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.96); I^2=0%					
Test for overall effect: Z=0.92(P=0.36)					
1.4.2 any antipsychotics in both groups					
A +any antipsychotic 2011	5/56	7/58		80.73%	0.74[0.25,2.19]
Subtotal (95% CI)	**56**	**58**		**80.73%**	**0.74[0.25,2.19]**
Total events: 5 (AP combination), 7 (AP monotherapy)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.54(P=0.59)					
Total (95% CI)	**101**	**101**		**100%**	**0.96[0.36,2.55]**
Total events: 7 (AP combination), 7 (AP monotherapy)					
Heterogeneity: Tau^2=0; Chi^2=1.16, df=2(P=0.56); I^2=0%					
Test for overall effect: Z=0.08(P=0.93)					
Test for subgroup differences: Chi^2=1.14, df=1 (P=0.29), I^2=12.35%					



Favours AP combination — Favours AP monotherapy

Analysis 1.5. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 5 Clinical response: 3. Global state - i. average severity score (CGI-S scale, high = bad).

Study or subgroup	AP combination N	AP combination Mean(SD)	AP monotherapy N	AP monotherapy Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.5.1 clozapine in both groups							
B +risperidone 2010	25	4.5 (0.8)	28	4.9 (0.8)		11.61%	-0.4[-0.83,0.03]
C +aripiprazole 2008	29	3.5 (0.9)	32	3.7 (0.7)		12.5%	-0.2[-0.61,0.21]
C +risperidone 2006	32	5 (1)	33	4.5 (1.1)		9.64%	0.51[0.02,1]
Subtotal ***	**86**		**93**			**33.74%**	**-0.04[-0.55,0.47]**
Heterogeneity: Tau^2=0.15; Chi^2=7.93, df=2(P=0.02); I^2=74.79%							
Test for overall effect: Z=0.17(P=0.86)							
1.5.2 other atypical drugs in both groups							
C +aripiprazole 2014	59	2.3 (0.4)	57	2.4 (0.5)		26.97%	-0.1[-0.26,0.06]
C +aripiprazole 2015	89	2.8 (1)	30	2.8 (1.1)		11.43%	-0.04[-0.48,0.4]
C +fluphen dec 2009	14	3.5 (0.4)	14	4 (0.7)		11.18%	-0.49[-0.93,-0.05]
Subtotal ***	**162**		**101**			**49.57%**	**-0.16[-0.37,0.05]**
Heterogeneity: Tau^2=0.01; Chi^2=2.82, df=2(P=0.24); I^2=29.14%							
Test for overall effect: Z=1.48(P=0.14)							
1.5.3 typical drugs in both groups							
C +aripiprazole 2007b	26	4.1 (0.4)	28	4.2 (0.7)		16.69%	-0.1[-0.42,0.22]
Subtotal ***	**26**		**28**			**16.69%**	**-0.1[-0.42,0.22]**

Favours AP combination — Favours AP monotherapy

Study or subgroup	AP combination N	AP combination Mean(SD)	AP monotherapy N	AP monotherapy Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Heterogeneity: Not applicable							
Test for overall effect: Z=0.62(P=0.54)							
Total ***	**274**		**222**			**100%**	**-0.13[-0.31,0.06]**
Heterogeneity: Tau²=0.02; Chi²=10.89, df=6(P=0.09); I²=44.93%							
Test for overall effect: Z=1.36(P=0.17)							
Test for subgroup differences: Chi²=0.22, df=1 (P=0.89), I²=0%							

Favours AP combination -5 -2.5 0 2.5 5 Favours AP monotherapy

Analysis 1.6. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 6 Clinical response: 3. Global state - ii. change in severity score (CGI-S scale, high = bad).

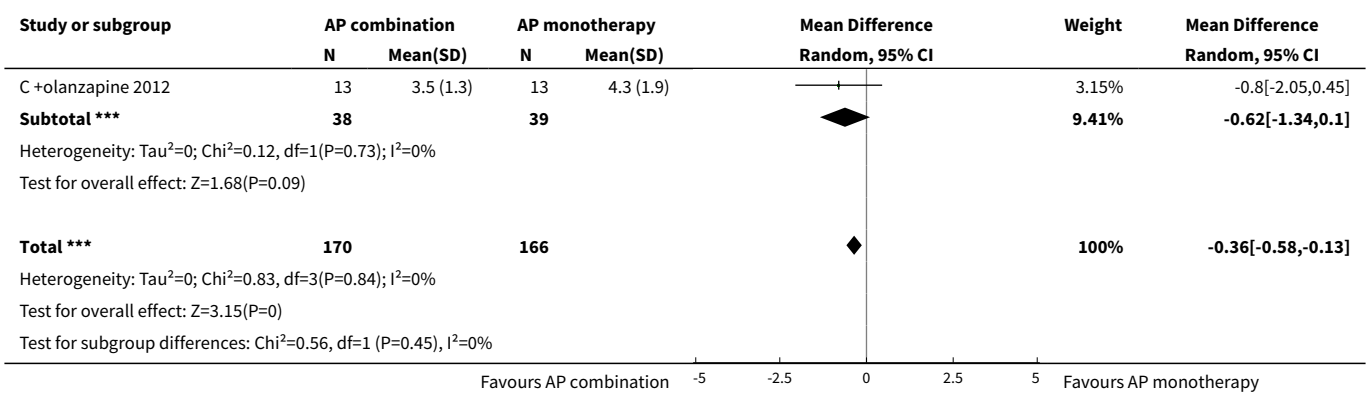
Study or subgroup	AP combination N	AP combination Mean(SD)	AP monotherapy N	AP monotherapy Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.6.1 clozapine in both groups							
C +pimozide 2011	25	-0.1 (0.6)	28	-0.3 (0.6)		45.17%	0.21[-0.09,0.51]
Subtotal ***	**25**		**28**			**45.17%**	**0.21[-0.09,0.51]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.35(P=0.18)							
1.6.2 other atypical drugs in both groups							
C +haloperidol 2010	46	-1.2 (0.8)	42	-1.2 (0.8)		37.41%	0[-0.33,0.33]
C +sulpiride 2013	46	-1.4 (1.2)	46	-1.5 (1.2)		17.42%	0.1[-0.39,0.59]
Subtotal ***	**92**		**88**			**54.83%**	**0.03[-0.24,0.31]**
Heterogeneity: Tau²=0; Chi²=0.11, df=1(P=0.74); I²=0%							
Test for overall effect: Z=0.23(P=0.82)							
Total ***	**117**		**116**			**100%**	**0.11[-0.09,0.32]**
Heterogeneity: Tau²=0; Chi²=0.83, df=2(P=0.66); I²=0%							
Test for overall effect: Z=1.08(P=0.28)							
Test for subgroup differences: Chi²=0.72, df=1 (P=0.4), I²=0%							

Favours AP combination -5 -2.5 0 2.5 5 Favours AP monotherapy

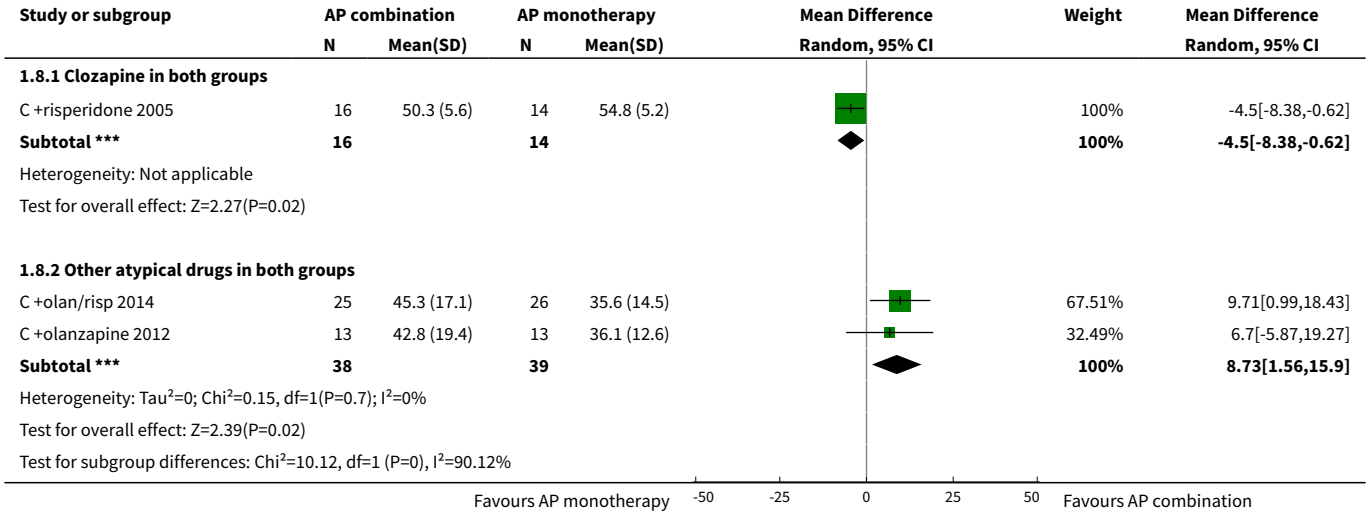
Analysis 1.7. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 7 Clinical response: 4. Global state - average improvement score (CGI-I scale, high = bad).

Study or subgroup	AP combination N	AP combination Mean(SD)	AP monotherapy N	AP monotherapy Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.7.1 clozapine in both groups							
B +aripiprazole 2008	107	3.2 (1)	99	3.5 (1)		64.12%	-0.3[-0.58,-0.02]
B +risperidone 2010	25	4.5 (0.8)	28	4.9 (0.8)		26.47%	-0.4[-0.83,0.03]
Subtotal ***	**132**		**127**			**90.59%**	**-0.33[-0.56,-0.1]**
Heterogeneity: Tau²=0; Chi²=0.15, df=1(P=0.7); I²=0%							
Test for overall effect: Z=2.77(P=0.01)							
1.7.2 other atypical drugs in both groups							
C +olan/risp 2014	25	3.7 (1.6)	26	4.2 (1.7)		6.27%	-0.53[-1.42,0.36]

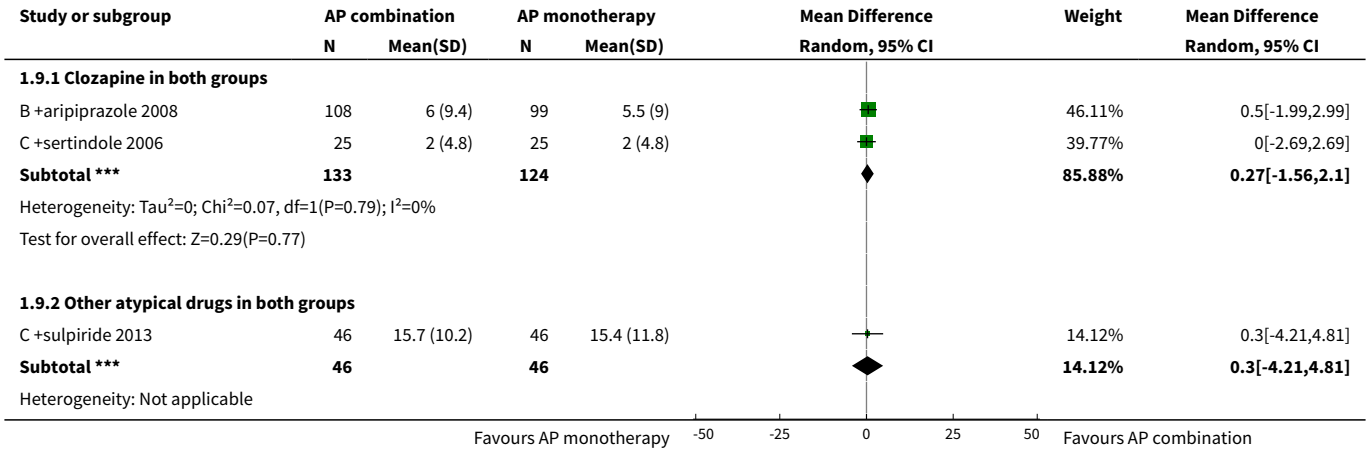
Favours AP combination -5 -2.5 0 2.5 5 Favours AP monotherapy



Analysis 1.8. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 8 Clinical response: 5. Global state - i. average functioning score (GAF scale, high = good).



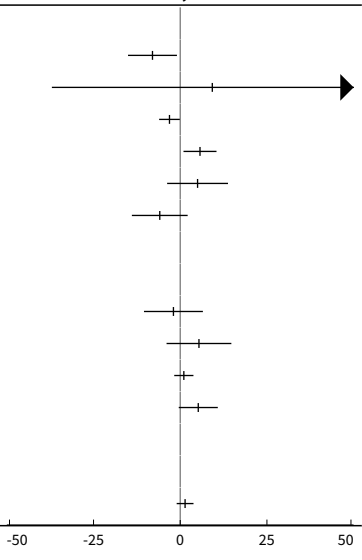
Analysis 1.9. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 9 Clinical response: 5. Global state - ii. change in functioning score (GAF scale, high = good).



Study or subgroup	AP combination N	AP combination Mean(SD)	AP monotherapy N	AP monotherapy Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for overall effect: Z=0.13(P=0.9)							
Total ***	**179**		**170**			**100%**	**0.27[-1.42,1.97]**
Heterogeneity: Tau²=0; Chi²=0.07, df=2(P=0.96); I²=0%							
Test for overall effect: Z=0.32(P=0.75)							
Test for subgroup differences: Chi²=0, df=1 (P=0.99), I²=0%							

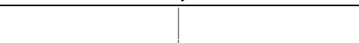
Analysis 1.10. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 10 Mental state: 1. Overall - a.i average total score (PANSS scale, high = bad).

Study or subgroup	AP combination N	AP combination Mean(SD)	AP monotherapy N	AP monotherapy Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
1.10.1 Clozapine in both groups						
B +ziprasidone 2014	20	63.2 (13.9)	20	71.2 (8.1)		-8[-15.05,-0.95]
C +haloperidol 2006	2	96.3 (30.3)	4	87 (19.8)		9.25[-37.01,55.51]
C +risperidone 2001	109	34.7 (11.1)	106	37.8 (11.2)		-3.1[-6.08,-0.12]
C +risperidone 2005	16	69.7 (6.6)	14	64 (6.7)		5.7[0.94,10.46]
C +risperidone 2006	32	89.8 (15.8)	33	84.8 (20.1)		5[-3.77,13.77]
C +risperidone 2007	11	69.2 (9.3)	13	75.1 (10.8)		-5.9[-13.94,2.14]
1.10.2 Other atypical drugs in both groups						
C +arip/pali 2014	60	85.9 (20.6)	30	87.8 (18.7)		-1.96[-10.45,6.53]
C +aripiprazole 2012	18	63.1 (17.4)	18	57.7 (10.3)		5.4[-3.94,14.74]
C +aripiprazole 2014	59	53.8 (8.7)	57	52.8 (6.4)		1.04[-1.73,3.81]
C +aripiprazole 2016	30	55.8 (12.9)	30	50.6 (9)		5.2[-0.43,10.83]
1.10.3 Any antipsychotic in both groups						
B +any antipsychotic 2013	19	17.3 (4.4)	20	15.9 (3.2)		1.4[-1.03,3.83]

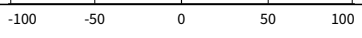


Analysis 1.11. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 11 Mental state: 1. Overall - a.ii change in total score (PANSS scale, high = bad).

Study or subgroup	AP combination N	AP combination Mean(SD)	AP monotherapy N	AP monotherapy Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.11.1 Clozapine in both groups							
C +aripiprazole 2013	16	-5.6 (8.8)	14	-2.6 (6.3)		19.06%	-3[-8.43,2.43]
C +pimozide 2011	25	-0.7 (10.6)	28	-3.6 (10.2)		17.9%	2.84[-2.76,8.44]
C +sertindole 2006	25	-6 (7.3)	25	-5 (7.3)		34.62%	-1[-5.03,3.03]
Subtotal ***	**66**		**67**			**71.58%**	**-0.55[-3.54,2.43]**
Heterogeneity: Tau²=0.76; Chi²=2.24, df=2(P=0.33); I²=10.54%							
Test for overall effect: Z=0.36(P=0.72)							
1.11.2 Other atypical drugs in both groups							
C +haloperidol 2010	46	-20.1 (20.4)	42	-22.2 (19.8)		7.96%	2.1[-6.3,10.5]
C +olan/risp 2014	25	-28.7 (25)	26	-17.6 (19.1)		3.76%	-11.06[-23.29,1.17]



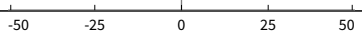
Study or subgroup	AP combination N	AP combination Mean(SD)	AP monotherapy N	AP monotherapy Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
C +olanzapine 2012	13	-25.9 (25.2)	13	-21.4 (22.8)		1.65%	-4.5[-22.97,13.97]
C +sulpiride 2004	8	-27.8 (15.3)	8	-21.4 (19.3)		1.93%	-6.4[-23.47,10.67]
C +sulpiride 2013	46	-17.1 (15.6)	46	-15.6 (16.4)		13.13%	-1.5[-8.04,5.04]
Subtotal ***	**138**		**135**			**28.42%**	**-2.26[-6.71,2.18]**
Heterogeneity: Tau²=0; Chi²=3.36, df=4(P=0.5); I²=0%							
Test for overall effect: Z=1(P=0.32)							
Total ***	**204**		**202**			**100%**	**-1.05[-3.42,1.32]**
Heterogeneity: Tau²=0; Chi²=5.99, df=7(P=0.54); I²=0%							
Test for overall effect: Z=0.87(P=0.38)							
Test for subgroup differences: Chi²=0.39, df=1 (P=0.53), I²=0%							



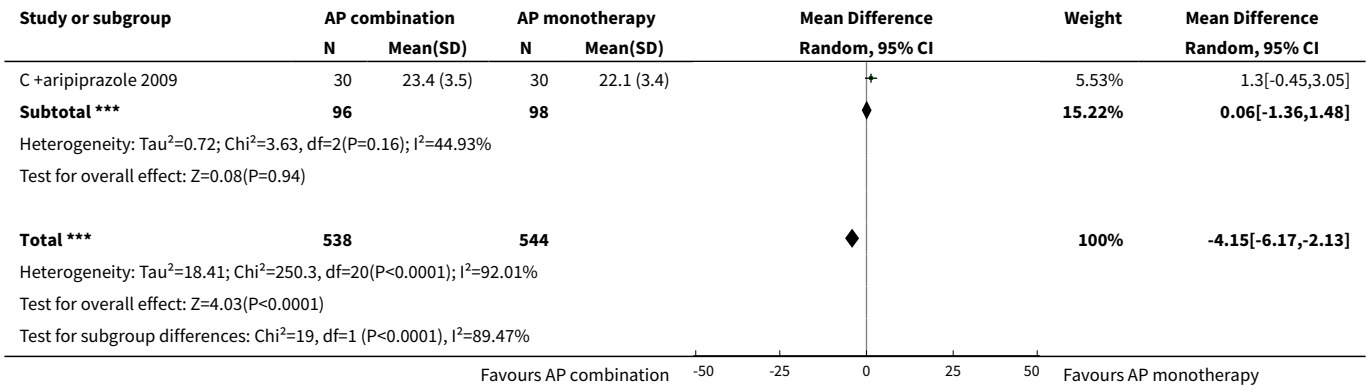
Favours AP combination — Favours AP monotherapy

Analysis 1.12. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 12 Mental state: 1. Overall - b.i. average total score (BPRS scale, high = bad).

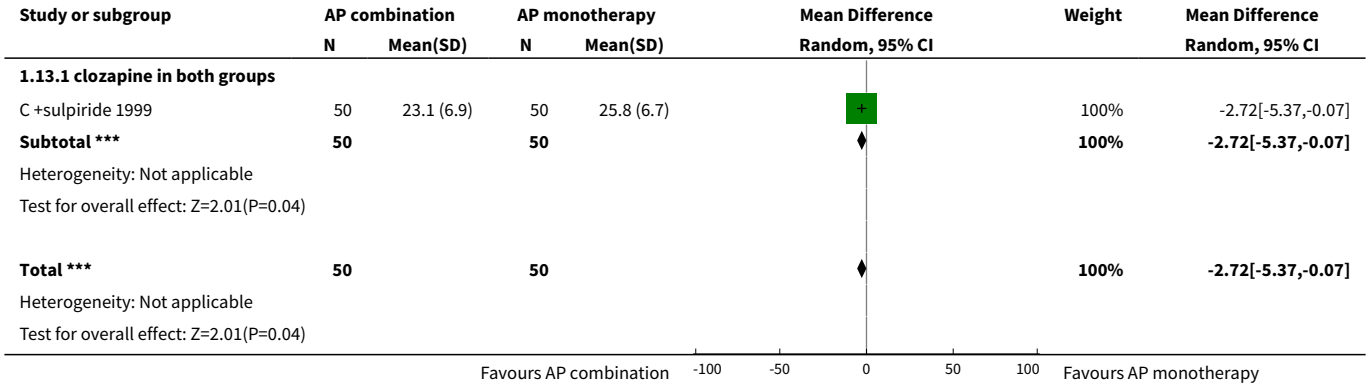
Study or subgroup	AP combination N	AP combination Mean(SD)	AP monotherapy N	AP monotherapy Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.12.1 clozapine in both groups							
B +aripiprazole 2011	14	27.8 (7.3)	17	36.4 (9.7)		3.83%	-8.6[-14.59,-2.61]
B +pipotiazine 2002	42	23.6 (6.4)	42	30.5 (6.1)		5.24%	-6.9[-9.57,-4.23]
B +risperidone 2010	25	36.4 (9.3)	28	41 (10.3)		4.14%	-4.6[-9.88,0.68]
B +sulpiride 1996	31	7.2 (4)	32	14.5 (3.6)		5.49%	-7.3[-9.18,-5.42]
B +ziprasidone 2014	20	35.3 (4.1)	20	38.1 (5.1)		5.17%	-2.8[-5.67,0.07]
C +aripiprazole 2008	29	42.5 (11)	32	43.8 (10.1)		4.12%	-1.3[-6.62,4.02]
C +CPZ 1989	20	35 (5)	17	39 (4)		5.15%	-4[-6.9,-1.1]
C +CPZ 1999	40	24.2 (6.2)	40	27 (5)		5.31%	-2.8[-5.27,-0.33]
C +pimozide 2013	14	39.6 (7.9)	14	37.9 (7.9)		3.9%	1.7[-4.12,7.52]
C +pipotiazine 2000	26	16.3 (3.8)	24	20.4 (3.5)		5.45%	-4.1[-6.12,-2.08]
C +risperidone 2001c	32	21.4 (7)	32	24.9 (6.7)		4.97%	-3.5[-6.86,-0.14]
C +risperidone 2005b	20	42.8 (11)	20	44.8 (10.1)		3.59%	-2[-8.54,4.54]
C +sulpiride 1997	16	-8.7 (8.3)	12	-2.3 (6.2)		4.1%	-6.4[-11.77,-1.03]
C +sulpiride 1999b	20	17.9 (3.1)	21	30 (3.2)		5.48%	-12.11[-14.03,-10.19]
C +sulpiride 1999c	29	23.4 (5.9)	30	26.8 (7.5)		4.94%	-3.4[-6.84,0.04]
C +sulpiride 2003	30	12.2 (3.8)	31	22.4 (3.5)		5.51%	-10.2[-12.03,-8.37]
Subtotal ***	**408**		**412**			**76.39%**	**-5.19[-7.08,-3.3]**
Heterogeneity: Tau²=11.22; Chi²=92.65, df=15(P<0.0001); I²=83.81%							
Test for overall effect: Z=5.39(P<0.0001)							
1.12.2 other atypical drugs in both groups							
C +clozapine 2001	20	25.4 (6.3)	20	23.6 (6.4)		4.73%	1.8[-2.15,5.75]
C +fluphen dec 2009	14	27.8 (7.3)	14	36.4 (9.7)		3.67%	-8.6[-14.96,-2.24]
Subtotal ***	**34**		**34**			**8.4%**	**-3.09[-13.26,7.08]**
Heterogeneity: Tau²=46.79; Chi²=7.42, df=1(P=0.01); I²=86.52%							
Test for overall effect: Z=0.6(P=0.55)							
1.12.3 typical drugs in both groups							
C +aripiprazole 2007b	26	41.6 (11)	28	43.3 (10.1)		3.98%	-1.7[-7.35,3.95]
C +aripiprazole 2008b	40	20.7 (1.8)	40	21.2 (1.9)		5.71%	-0.5[-1.31,0.31]



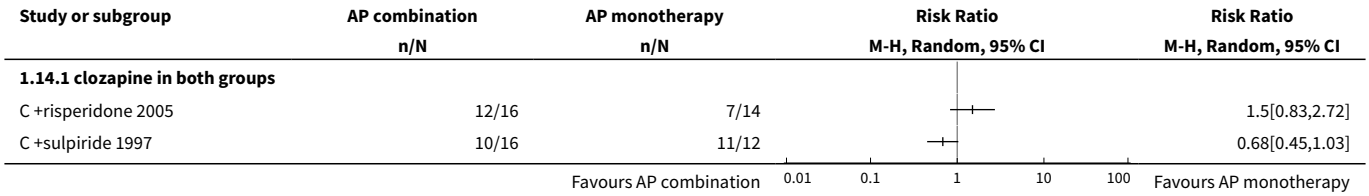
Favours AP combination — Favours AP monotherapy



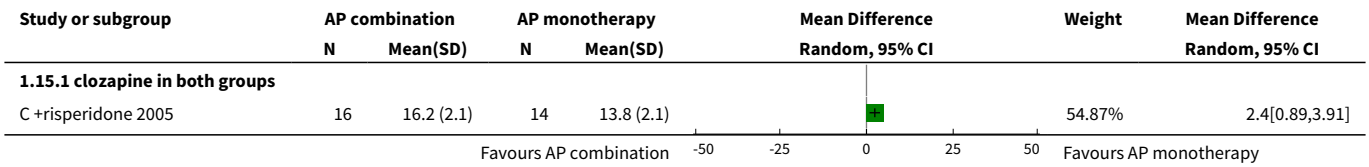
Analysis 1.13. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 13 Mental state: 1. Overall - b.ii change total score (BPRS scale, high = bad).



Analysis 1.14. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 14 Mental state: 2. Specific - a. positive symptoms - no clinical improvement.



Analysis 1.15. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 15 Mental state: 2. Specific - b. positive symptoms - i. average score (PANSS scale, high = bad).



Study or subgroup	AP combination N	AP combination Mean(SD)	AP monotherapy N	AP monotherapy Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
C +risperidone 2006	32	20.4 (5.7)	33	18.4 (5.4)		17.18%	2[-0.7,4.7]
C +risperidone 2007	13	18.6 (4.9)	11	17.7 (5.8)		6.65%	0.9[-3.44,5.24]
Subtotal ***	**61**		**58**			**78.69%**	**2.19[0.92,3.45]**
Heterogeneity: Tau^2=0; Chi^2=0.43, df=2(P=0.81); I^2=0%							
Test for overall effect: Z=3.4(P=0)							
1.15.2 any antipsychotics in both groups							
B +any antipsychotic 2013	19	17.3 (4.4)	20	15.9 (3.2)		21.31%	1.4[-1.03,3.83]
Subtotal ***	**19**		**20**			**21.31%**	**1.4[-1.03,3.83]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.13(P=0.26)							
Total ***	**80**		**78**			**100%**	**2.02[0.9,3.14]**
Heterogeneity: Tau^2=0; Chi^2=0.75, df=3(P=0.86); I^2=0%							
Test for overall effect: Z=3.53(P=0)							
Test for subgroup differences: Chi^2=0.32, df=1 (P=0.57), I^2=0%							

Favours AP combination — Favours AP monotherapy

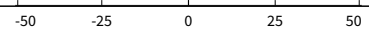
Analysis 1.16. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 16 Mental state: 2. Specific - b. positive symptoms - ii. change score (PANSS scale, high = bad).

Study or subgroup	AP combination N	AP combination Mean(SD)	AP monotherapy N	AP monotherapy Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.16.1 clozapine in both groups							
B +aripiprazole 2008	106	-2.2 (3.1)	99	-1.7 (3)		30.39%	-0.5[-1.33,0.33]
C +pimozide 2011	25	-1.3 (2.6)	28	-1 (3)		9.44%	-0.25[-1.74,1.24]
C +sertindole 2006	25	-2 (4.8)	25	-2 (2.4)		4.66%	0[-2.12,2.12]
Subtotal ***	**156**		**152**			**44.49%**	**-0.39[-1.08,0.29]**
Heterogeneity: Tau^2=0; Chi^2=0.23, df=2(P=0.89); I^2=0%							
Test for overall effect: Z=1.13(P=0.26)							
1.16.2 other atypical drugs in both groups							
B +quet/risp 2009	160	-2.6 (3.1)	150	-3.1 (3)		45.96%	0.5[-0.18,1.18]
C +haloperidol 2010	46	-6.3 (6.5)	42	-7.2 (6)		3.08%	0.9[-1.71,3.51]
C +olan/risp 2014	25	-9.6 (8.1)	26	-6.5 (6.3)		1.31%	-3.07[-7.08,0.94]
C +olanzapine 2012	13	-10.1 (9.4)	13	-10.1 (9)		0.42%	0[-7.07,7.07]
C +sulpiride 2004	8	-8.4 (6)	8	-6.6 (7.9)		0.44%	-1.8[-8.67,5.07]
C +sulpiride 2013	46	-6.4 (5.8)	46	-5.8 (5)		4.29%	-0.6[-2.81,1.61]
Subtotal ***	**298**		**285**			**55.51%**	**0.33[-0.28,0.95]**
Heterogeneity: Tau^2=0; Chi^2=4.25, df=5(P=0.51); I^2=0%							
Test for overall effect: Z=1.05(P=0.29)							
Total ***	**454**		**437**			**100%**	**0.01[-0.45,0.47]**
Heterogeneity: Tau^2=0; Chi^2=6.85, df=8(P=0.55); I^2=0%							
Test for overall effect: Z=0.03(P=0.97)							
Test for subgroup differences: Chi^2=2.38, df=1 (P=0.12), I^2=57.9%							

Favours AP combination — Favours AP monotherapy

Analysis 1.17. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 17 Mental state: 2. Specific - b. positive symptoms - iii. average score (BPRS scale, high = bad).

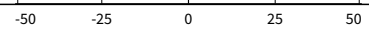
Study or subgroup	AP combination N	AP combination Mean(SD)	AP monotherapy N	AP monotherapy Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.17.1 clozapine in both groups							
B +risperidone 2010	25	13.2 (3.5)	28	14.1 (3.6)		32.21%	-0.9[-2.81,1.01]
C +risperidone 2005b	20	12.8 (3.5)	20	15.4 (3.6)		26.99%	-2.6[-4.8,-0.4]
Subtotal ***	**45**		**48**			**59.2%**	**-1.66[-3.32,-0]**
Heterogeneity: Tau^2=0.34; Chi^2=1.31, df=1(P=0.25); I^2=23.41%							
Test for overall effect: Z=1.96(P=0.05)							
1.17.2 other atypical drugs in both groups							
C +clozapine 2001	20	6.2 (2.4)	20	6.3 (2.5)		40.8%	-0.07[-1.61,1.47]
Subtotal ***	**20**		**20**			**40.8%**	**-0.07[-1.61,1.47]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.09(P=0.93)							
Total ***	**65**		**68**			**100%**	**-1.02[-2.42,0.38]**
Heterogeneity: Tau^2=0.64; Chi^2=3.41, df=2(P=0.18); I^2=41.31%							
Test for overall effect: Z=1.42(P=0.15)							
Test for subgroup differences: Chi^2=1.9, df=1 (P=0.17), I^2=47.28%							



Favours AP combination — Favours AP monotherapy

Analysis 1.18. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 18 Mental state: 2. Specific - b. positive symptoms - iv. change data (BPRS scale, high = bad).

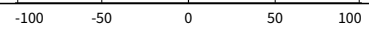
Study or subgroup	AP combination N	AP combination Mean(SD)	AP monotherapy N	AP monotherapy Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.18.1 typical drugs in both groups							
C +levomepromazine 2004	9	-1.4 (1.2)	8	-1.1 (0.5)		100%	-0.3[-1.16,0.56]
Subtotal ***	**9**		**8**			**100%**	**-0.3[-1.16,0.56]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.69(P=0.49)							
Total ***	**9**		**8**			**100%**	**-0.3[-1.16,0.56]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.69(P=0.49)							



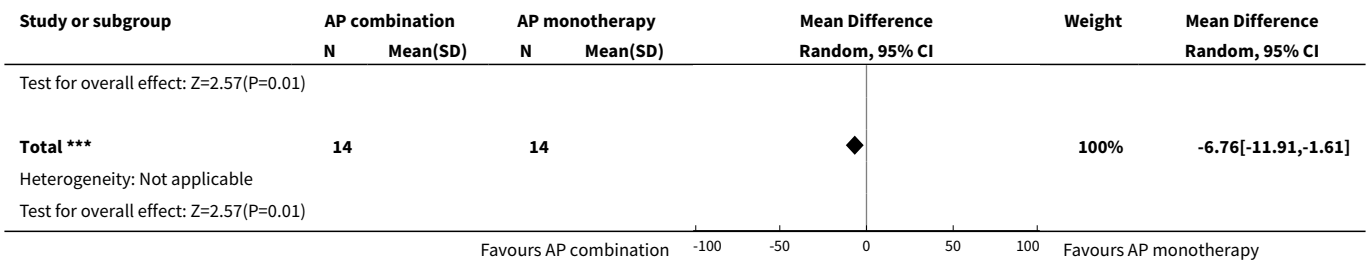
Favours AP combination — Favours AP monotherapy

Analysis 1.19. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 19 Mental state: 2. Specific - b. positive symptoms - v. average score (SAPS scale, high = bad).

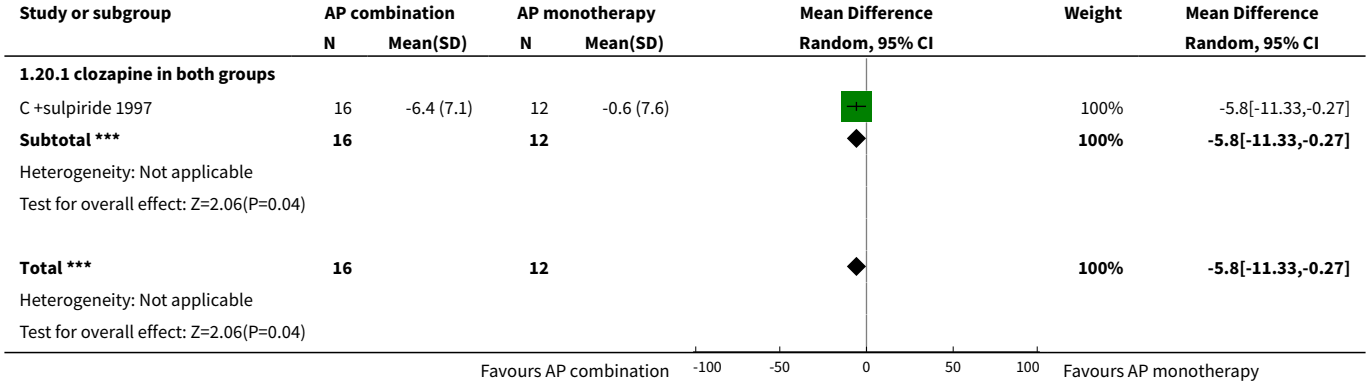
Study or subgroup	AP combination N	AP combination Mean(SD)	AP monotherapy N	AP monotherapy Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.19.1 other atypical drugs in both groups							
C +fluphen dec 2009	14	73.2 (7.3)	14	79.9 (6.6)		100%	-6.76[-11.91,-1.61]
Subtotal ***	**14**		**14**			**100%**	**-6.76[-11.91,-1.61]**
Heterogeneity: Not applicable							



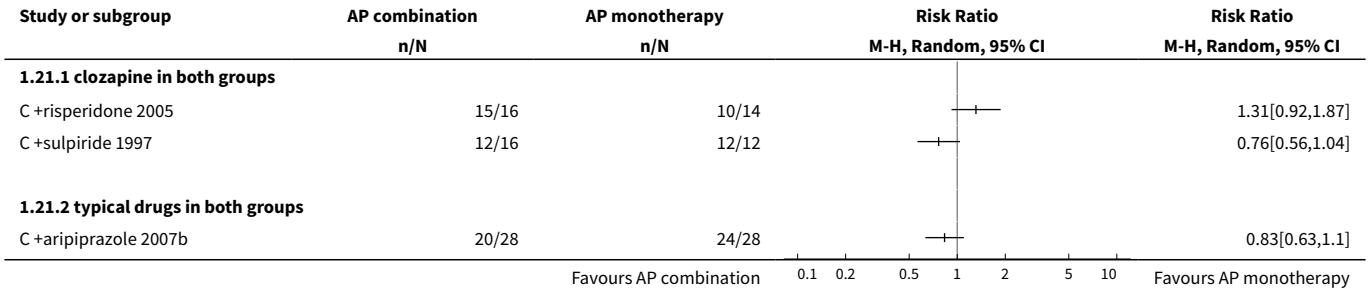
Favours AP combination — Favours AP monotherapy



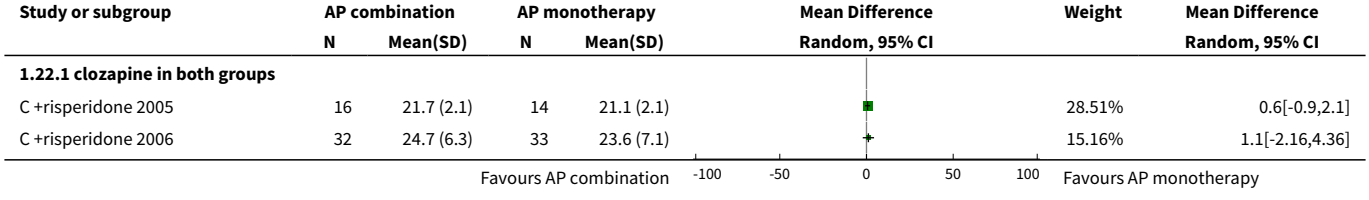
Analysis 1.20. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 20 Mental state: 2. Specific - b. positive symptoms - vi. change score (SAPS scale, high = bad).



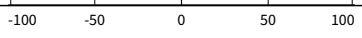
Analysis 1.21. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 21 Mental state: 3. Specific - a. negative symptoms - no clinical improvement.



Analysis 1.22. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 22 Mental state: 3. Specific - b. negative symptoms - i. average score (PANSS scale, high = bad).



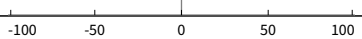
Study or subgroup	AP combination N	AP combination Mean(SD)	AP monotherapy N	AP monotherapy Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
C +risperidone 2007	11	18.5 (5)	13	21.1 (5.4)		11.03%	-2.6[-6.77,1.57]
Subtotal ***	**59**		**60**			**54.7%**	**0.31[-1.18,1.8]**
Heterogeneity: Tau²=0.25; Chi²=2.24, df=2(P=0.33); I²=10.57%							
Test for overall effect: Z=0.41(P=0.68)							
1.22.2 other atypical drugs in both groups							
C +aripiprazole 2012	18	14.8 (5.1)	18	13.6 (2.9)		18.57%	1.2[-1.51,3.91]
Subtotal ***	**18**		**18**			**18.57%**	**1.2[-1.51,3.91]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.87(P=0.39)							
1.22.3 Any antipsychotic in both groups							
B +any antipsychotic 2013	19	20.6 (2.7)	20	17.3 (2.7)		26.74%	3.3[1.6,5]
Subtotal ***	**19**		**20**			**26.74%**	**3.3[1.6,5]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.82(P=0)							
Total ***	**96**		**98**			**100%**	**1.16[-0.49,2.8]**
Heterogeneity: Tau²=1.9; Chi²=9.52, df=4(P=0.05); I²=57.97%							
Test for overall effect: Z=1.38(P=0.17)							
Test for subgroup differences: Chi²=6.83, df=1 (P=0.03), I²=70.73%							



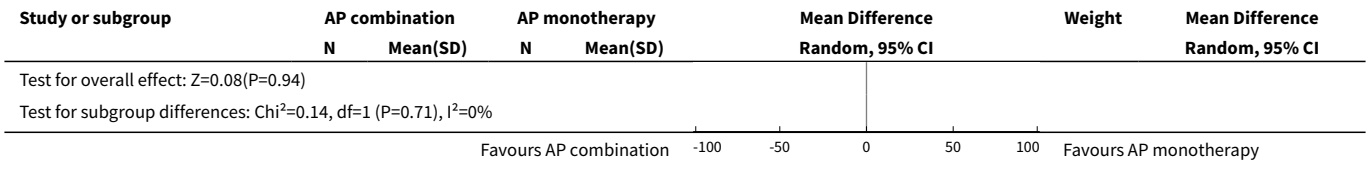
Favours AP combination — Favours AP monotherapy

Analysis 1.23. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 23 Mental state: 3. Specific - b. negative symptoms - ii. change score (PANSS scale, high = bad).

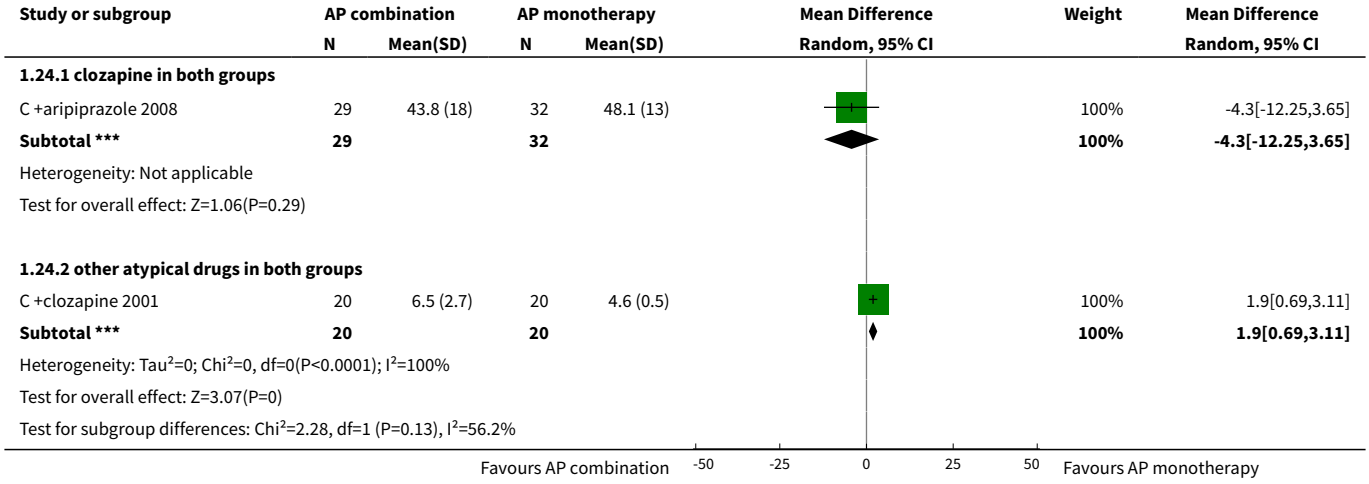
Study or subgroup	AP combination N	AP combination Mean(SD)	AP monotherapy N	AP monotherapy Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.23.1 clozapine in both groups							
B +aripiprazole 2008	106	-1.9 (4.1)	99	-1.5 (4)		25.32%	-0.4[-1.51,0.71]
C +pimozide 2011	25	0.7 (4.7)	28	-1.6 (4.5)		5.14%	2.24[-0.22,4.7]
C +sertindole 2006	25	-1 (2.4)	25	-1 (4.8)		6.9%	0[-2.12,2.12]
Subtotal ***	**156**		**152**			**37.37%**	**0.31[-1.11,1.74]**
Heterogeneity: Tau²=0.75; Chi²=3.68, df=2(P=0.16); I²=45.63%							
Test for overall effect: Z=0.43(P=0.67)							
1.23.2 other atypical drugs in both groups							
B +quet/risp 2009	160	-1.8 (4.1)	150	-1.9 (4)		38.29%	0.1[-0.8,1]
C +haloperidol 2010	46	-4.3 (4.9)	42	-4 (5.2)		6.95%	-0.3[-2.42,1.82]
C +olan/risp 2014	25	-10.7 (8.9)	26	-10.3 (12.2)		0.91%	-0.38[-6.22,5.46]
C +olanzapine 2012	13	-4.2 (5.6)	13	-2.9 (6.1)		1.54%	-1.3[-5.8,3.2]
C +sulpiride 2004	8	-6.6 (5.2)	8	-3.5 (3.4)		1.68%	-3.1[-7.41,1.21]
C +sulpiride 2013	46	-2.3 (3.1)	46	-2.8 (4.3)		13.26%	0.5[-1.03,2.03]
Subtotal ***	**298**		**285**			**62.63%**	**0.01[-0.69,0.72]**
Heterogeneity: Tau²=0; Chi²=2.86, df=5(P=0.72); I²=0%							
Test for overall effect: Z=0.04(P=0.97)							
Total ***	**454**		**437**			**100%**	**0.02[-0.54,0.58]**
Heterogeneity: Tau²=0; Chi²=6.54, df=8(P=0.59); I²=0%							



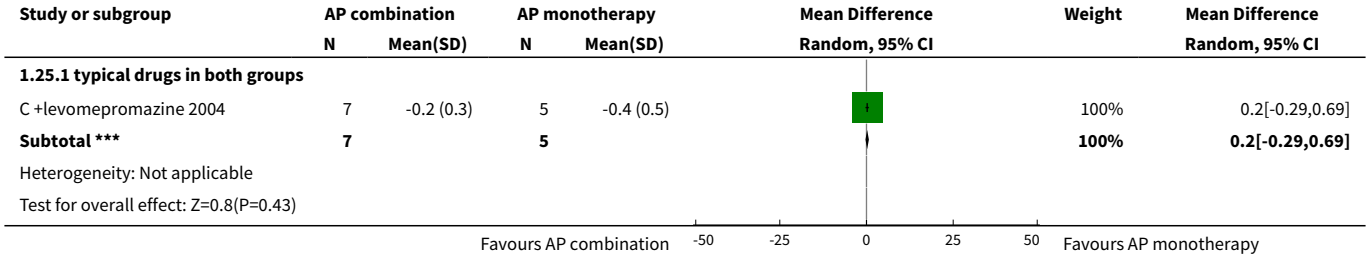
Favours AP combination — Favours AP monotherapy



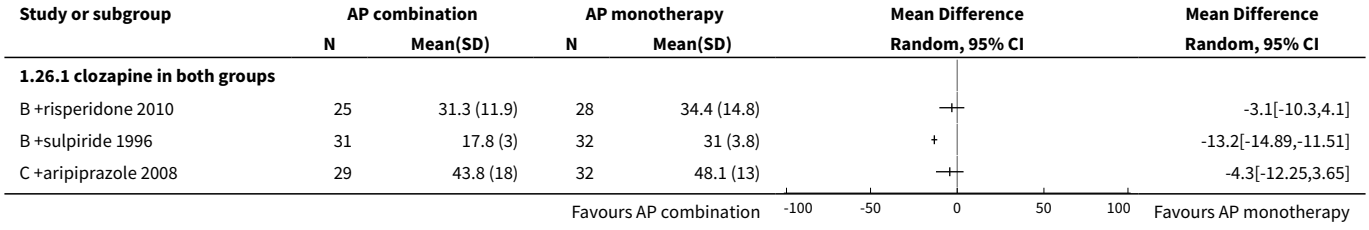
Analysis 1.24. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 24 Mental state: 3. Specific - b. negative symptoms - iii. average score (BPRS scale, high = bad).



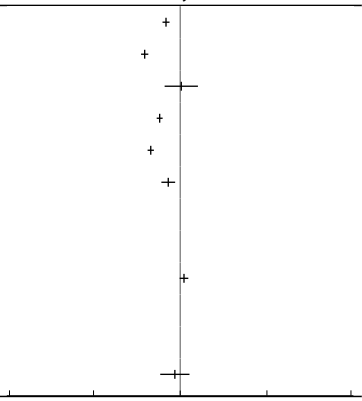
Analysis 1.25. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 25 Mental state: 3. Specific - b. negative symptoms - iv. change score (BPRS scale, high = bad).



Analysis 1.26. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 26 Mental state: 3. Specific - b. negative symptoms - v. average score (SANS scale, high = bad).

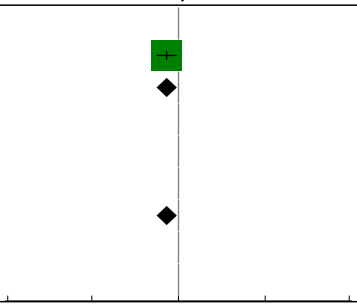


Study or subgroup	AP combination N	AP combination Mean(SD)	AP monotherapy N	AP monotherapy Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
C +pipotiazine 2000	26	21.3 (3.2)	24	29.5 (4)		-8.2[-10.22,-6.18]
C +risperidone 2005b	20	55.5 (3.6)	20	76 (3.1)		-20.5[-22.59,-18.41]
C +risperidone 2007	11	38.3 (10.9)	13	37.7 (13.1)		0.6[-9,10.2]
C +sulpiride 1999b	20	6 (2.3)	21	17.8 (3.2)		-11.86[-13.57,-10.15]
C +sulpiride 2003	30	19.3 (3.2)	31	36.3 (4)		-17[-18.81,-15.19]
C +sulpiride 2006	32	27.7 (8.3)	32	34.6 (7.9)		-6.9[-10.87,-2.93]
1.26.2 other atypical drugs in both groups						
C +fluphen dec 2009	14	65.1 (3.6)	14	63 (3.1)		2.17[-0.32,4.66]
1.26.3 typical drugs in both groups						
C +aripiprazole 2007b	26	49.8 (18)	28	52.9 (13)		-3.1[-11.53,5.33]



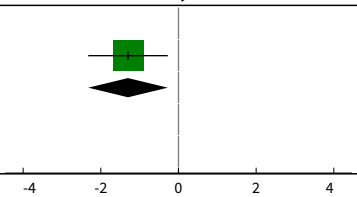
Analysis 1.27. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 27 Mental state: 3. Specific - b. negative symptoms - vi. average score (SANS scale, high = bad).

Study or subgroup	AP combination N	AP combination Mean(SD)	AP monotherapy N	AP monotherapy Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.27.1 clozapine in both groups							
C +sulpiride 1997	16	-8.3 (10.8)	12	-1.5 (4.4)		100%	-6.8[-12.65,-0.95]
Subtotal ***	**16**		**12**			**100%**	**-6.8[-12.65,-0.95]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.28(P=0.02)							
Total ***	**16**		**12**			**100%**	**-6.8[-12.65,-0.95]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.28(P=0.02)							



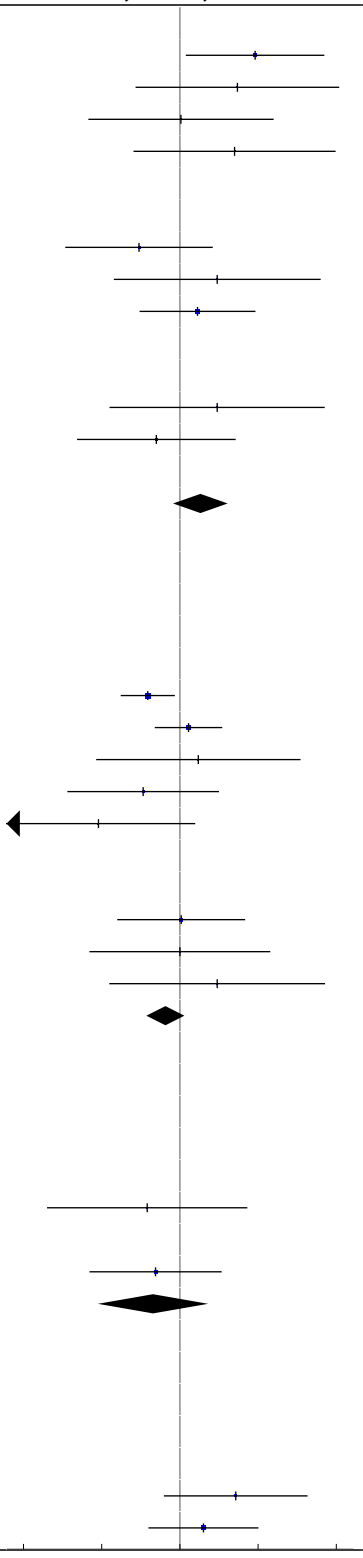
Analysis 1.28. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 28 Mental state: 4. Specific - aggression/agitation - average score (BPRS scale, high = bad).

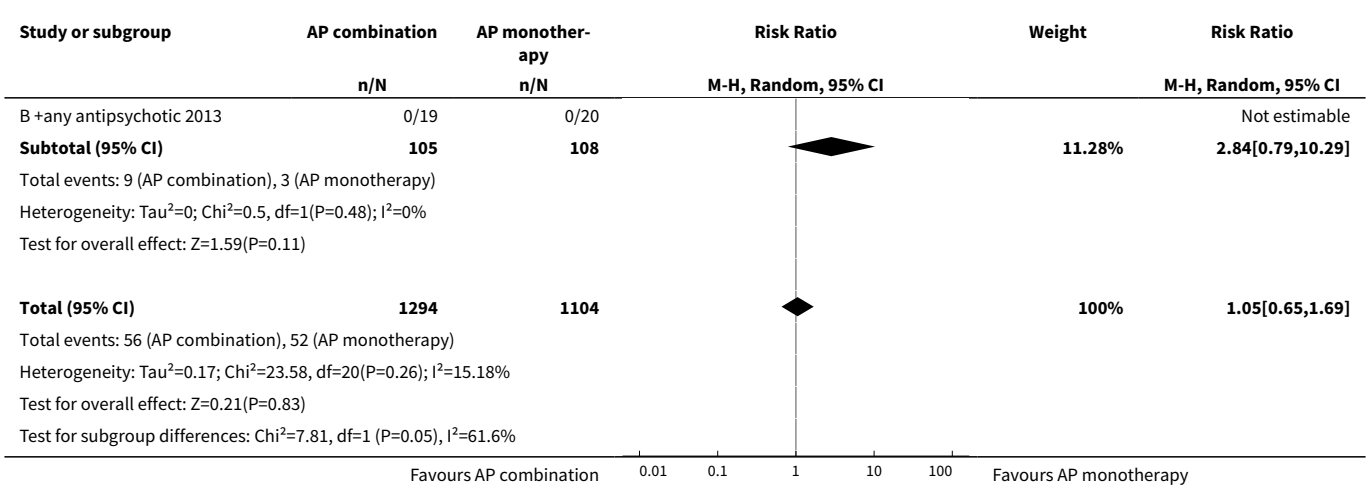
Study or subgroup	AP combination N	AP combination Mean(SD)	AP monotherapy N	AP monotherapy Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.28.1 typical drugs in both groups							
C +levomepromazine 2004	7	-1.8 (1.3)	5	-0.5 (0.4)		100%	-1.3[-2.32,-0.28]
Subtotal ***	**7**		**5**			**100%**	**-1.3[-2.32,-0.28]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.49(P=0.01)							



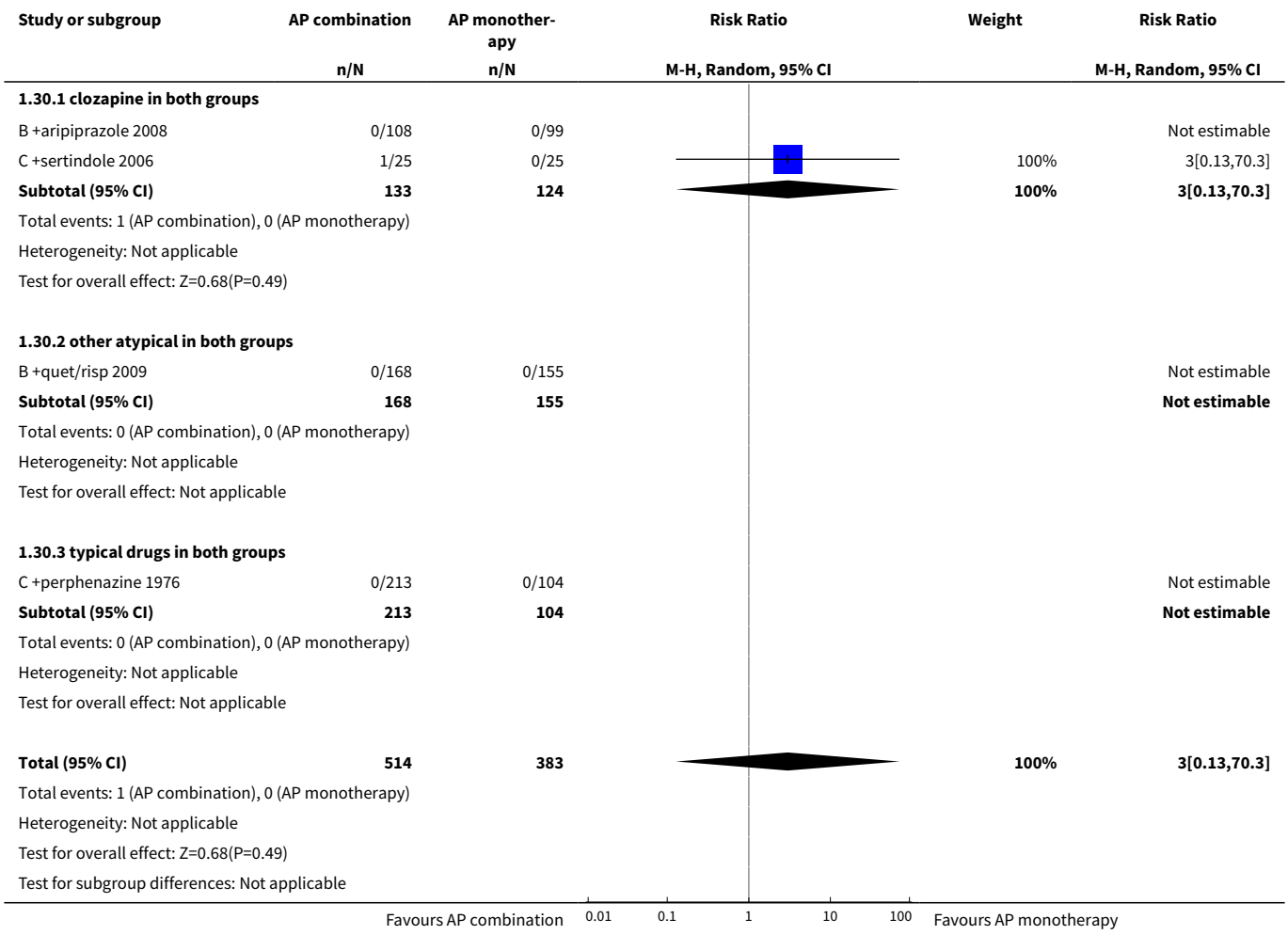
Analysis 1.29. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 29 Adverse events: 1. General - a. serious event or requiring discontinuation.

Study or subgroup	AP combination n/N	AP monotherapy n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.29.1 clozapine in both groups					
B +aripiprazole 2008	10/108	1/99		4.7%	9.17[1.19,70.32]
B +risperidone 2010	2/33	0/36		2.34%	5.44[0.27,109.34]
B +sulpiride 1996	1/31	1/32		2.79%	1.03[0.07,15.79]
B +ziprasidone 2014	2/20	0/20		2.38%	5[0.26,98]
C +amisulpride 2008	0/13	0/3			Not estimable
C +aripiprazole 2008	0/30	0/32			Not estimable
C +aripiprazole 2013	1/20	3/18		4.21%	0.3[0.03,2.63]
C +olanzapine 2012b	1/7	0/7		2.28%	3[0.14,63.15]
C +pimozide 2011	3/25	2/28		6.33%	1.68[0.31,9.25]
C +pimozide 2013	0/14	0/14			Not estimable
C +risperidone 2005	0/16	0/14			Not estimable
C +risperidone 2006	1/34	0/34		2.12%	3[0.13,71.15]
C +sertindole 2006	1/25	2/25		3.7%	0.5[0.05,5.17]
C +sulpiride 1997	0/16	0/12			Not estimable
Subtotal (95% CI)	**392**	**374**		**30.83%**	**1.83[0.82,4.08]**
Total events: 22 (AP combination), 9 (AP monotherapy)					
Heterogeneity: Tau^2=0; Chi^2=7.73, df=8(P=0.46); I^2=0%					
Test for overall effect: Z=1.47(P=0.14)					
1.29.2 other atypical in both groups					
B +quet/risp 2009	8/168	19/155		17.39%	0.39[0.18,0.86]
C +aripiprazole 2014	8/59	6/57		13.68%	1.29[0.48,3.48]
C +aripiprazole 2015	2/89	0/30		2.33%	1.72[0.08,34.9]
C +aripiprazole 2015c	1/56	3/57		4%	0.34[0.04,3.16]
C +aripiprazole 2016	0/30	5/30		2.57%	0.09[0.01,1.57]
C +fluphen dec 2009	0/14	0/14			Not estimable
C +haloperidol 2010	0/46	0/42			Not estimable
C +olan/risp 2014	2/25	2/26		5.38%	1.04[0.16,6.83]
C +olanzapine 2012	1/13	1/13		2.92%	1[0.07,14.34]
C +sulpiride 2013	1/46	0/46		2.11%	3[0.13,71.78]
Subtotal (95% CI)	**546**	**470**		**50.38%**	**0.65[0.37,1.14]**
Total events: 23 (AP combination), 36 (AP monotherapy)					
Heterogeneity: Tau^2=0.03; Chi^2=7.3, df=7(P=0.4); I^2=4.07%					
Test for overall effect: Z=1.49(P=0.14)					
1.29.3 typical drugs in both groups					
A +reserpine 1957	0/10	2/20		2.42%	0.38[0.02,7.28]
C +aripiprazole 2007b	0/28	0/28			Not estimable
C +perphenazine 1976	2/213	2/104		5.08%	0.49[0.07,3.42]
Subtotal (95% CI)	**251**	**152**		**7.5%**	**0.45[0.09,2.3]**
Total events: 2 (AP combination), 4 (AP monotherapy)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.89); I^2=0%					
Test for overall effect: Z=0.96(P=0.34)					
1.29.4 any antipsychotics in both groups					
A +any antipsychotic 2011	5/56	1/58		4.4%	5.18[0.62,42.95]
A +any antipsychotic 2012	4/30	2/30		6.88%	2[0.4,10.11]



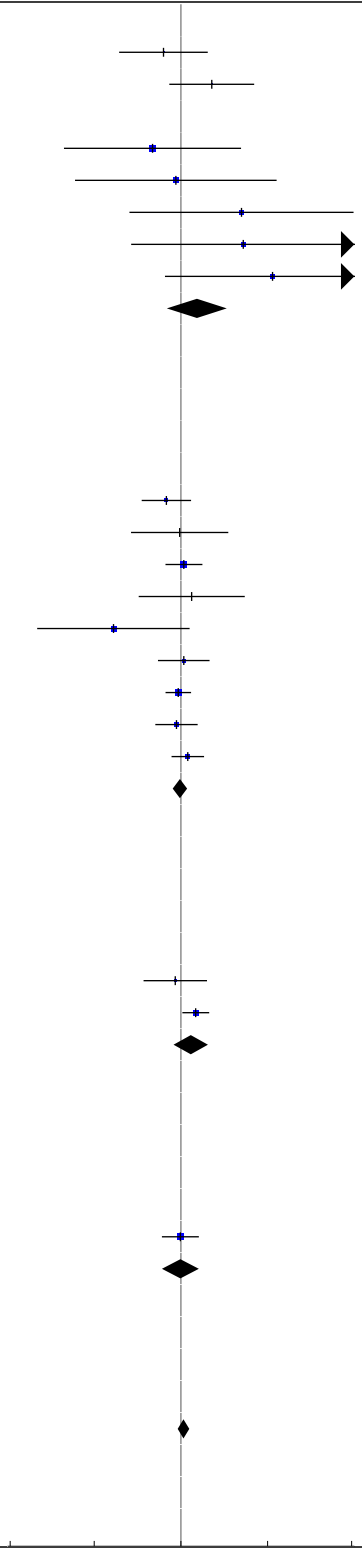


Analysis 1.30. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 30 Adverse events: 1. General - b. death (suicide or non-suicide deaths).

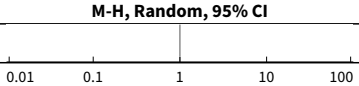


Analysis 1.31. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 31 Adverse events: 2. Movement disorders - a. any.

Study or subgroup	AP combination n/N	AP monotherapy n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.31.1 clozapine in both groups					
A +sulpiride 1994	4/36	6/34		1.71%	0.63[0.19,2.04]
B +aripiprazole 2008	10/108	4/98		1.85%	2.27[0.74,7]
B +aripiprazole 2011	0/14	0/17			Not estimable
C +risperidone 2001b	1/34	2/32		0.43%	0.47[0.04,4.94]
C +risperidone 2005	1/16	1/14		0.33%	0.88[0.06,12.73]
C +risperidone 2005b	2/20	0/20		0.27%	5[0.26,98]
C +sulpiride 1999b	2/20	0/21		0.27%	5.24[0.27,102.81]
C +sulpiride 2003	5/30	0/31		0.29%	11.35[0.66,196.81]
Subtotal (95% CI)	**278**	**267**		**5.14%**	**1.53[0.69,3.38]**
Total events: 25 (AP combination), 13 (AP monotherapy)					
Heterogeneity: Tau^2=0.19; Chi^2=7.19, df=6(P=0.3); I^2=16.52%					
Test for overall effect: Z=1.04(P=0.3)					
1.31.2 other atypical in both groups					
B +quet/risp 2009	14/168	19/155		5.47%	0.68[0.35,1.31]
C +aripiprazole 2007	4/31	4/30		1.41%	0.97[0.27,3.52]
C +aripiprazole 2015c	21/54	19/53		9.68%	1.08[0.66,1.77]
C +aripiprazole 2016	4/30	3/30		1.19%	1.33[0.33,5.45]
C +clozapine 2001	1/20	6/20		0.58%	0.17[0.02,1.26]
C +haloperidol 2010	13/46	11/42		5%	1.08[0.54,2.14]
C +olan/risp 2014	17/24	19/25		20.25%	0.93[0.66,1.31]
C +olanzapine 2012	8/13	9/13		7.41%	0.89[0.51,1.56]
C +sulpiride 2013	24/46	20/46		12.6%	1.2[0.78,1.85]
Subtotal (95% CI)	**432**	**414**		**63.59%**	**0.97[0.8,1.18]**
Total events: 106 (AP combination), 110 (AP monotherapy)					
Heterogeneity: Tau^2=0; Chi^2=5.71, df=8(P=0.68); I^2=0%					
Test for overall effect: Z=0.27(P=0.79)					
1.31.3 typical drugs in both groups					
C +CPZ 1973	5/15	12/31		3.32%	0.86[0.37,2]
C +perphenazine 1976	85/213	28/104		18.22%	1.48[1.04,2.12]
Subtotal (95% CI)	**228**	**135**		**21.54%**	**1.3[0.82,2.05]**
Total events: 90 (AP combination), 40 (AP monotherapy)					
Heterogeneity: Tau^2=0.04; Chi^2=1.36, df=1(P=0.24); I^2=26.35%					
Test for overall effect: Z=1.12(P=0.26)					
1.31.4 any antipsychotics in both groups					
A +any antipsychotic 2011	20/56	21/58		9.74%	0.99[0.6,1.61]
Subtotal (95% CI)	**56**	**58**		**9.74%**	**0.99[0.6,1.61]**
Total events: 20 (AP combination), 21 (AP monotherapy)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.05(P=0.96)					
Total (95% CI)	**994**	**874**		**100%**	**1.07[0.92,1.25]**
Total events: 241 (AP combination), 184 (AP monotherapy)					
Heterogeneity: Tau^2=0; Chi^2=18.08, df=18(P=0.45); I^2=0.42%					
Test for overall effect: Z=0.87(P=0.39)					



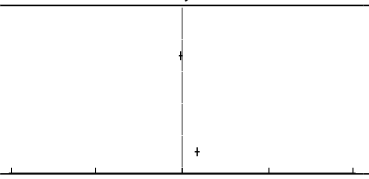
Study or subgroup	AP combination	AP monotherapy	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Test for subgroup differences: Chi²=2.28, df=1 (P=0.52), I²=0%					



Favours AP combination | Favours AP monotherapy

Analysis 1.32. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 32 Adverse events: 2. Movement disorders - b.i. average scores (SAS, high = bad).

Study or subgroup	AP combination		AP monotherapy		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
1.32.1 clozapine in both groups						
C +risperidone 2005	16	12.3 (1.5)	14	13.2 (1.5)		-0.9[-1.97,0.17]
1.32.2 other atypical drugs in both groups						
C +fluphen dec 2009	14	13.4 (2.5)	14	4.8 (1.1)		8.63[7.19,10.07]



Favours AP combination | Favours AP monotherapy

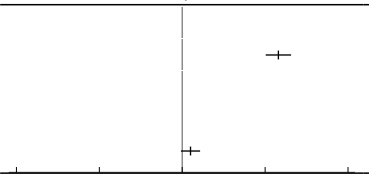
Analysis 1.33. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 33 Adverse events: 2. Movement disorders - b.ii. change scores (SAS, high = bad).

Study or subgroup	AP combination		AP monotherapy		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
1.33.1 other atypical drugs in both groups						
C +sulpiride 2013	31	0 (2)	32	0.5 (1.8)		-0.5[-1.44,0.44]

Favours AP combination | Favours AP monotherapy

Analysis 1.34. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 34 Adverse events: 2. Movement disorders - b.iii. average scores (TESS, high = bad).

Study or subgroup	AP combination		AP monotherapy		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
1.34.1 clozapine in both groups						
C +CPZ 1999	40	15.6 (2.1)	40	9.8 (1.3)		5.8[5.03,6.57]
1.34.2 other atypical drugs in both groups						
C +aripiprazole 2007	31	5.4 (1.2)	30	4.9 (1.1)		0.5[-0.08,1.08]



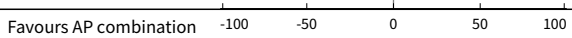
Favours AP combination | Favours AP monotherapy

Analysis 1.35. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 35 Adverse events: 2. Movement disorders - b.iv. average scores (DIEPSS, high = bad).

Study or subgroup	AP combination N	AP combination Mean(SD)	AP monotherapy N	AP monotherapy Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.35.1 clozapine in both groups							
C +aripiprazole 2008	29	3.6 (1.9)	32	3.3 (1.1)		100%	0.3[-0.49,1.09]
Subtotal ***	**29**		**32**			**100%**	**0.3[-0.49,1.09]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.74(P=0.46)							
Total ***	**29**		**32**			**100%**	**0.3[-0.49,1.09]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.74(P=0.46)							

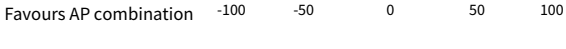
Analysis 1.36. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 36 Adverse events: 2. Movement disorders - b.v. change scores (BAS, high = bad).

Study or subgroup	AP combination N	AP combination Mean(SD)	AP monotherapy N	AP monotherapy Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.36.1 Other atypical drugs in both groups							
C +aripiprazole 2015b	15	0 (0)	13	0 (0)			Not estimable
C +sulpiride 2013	31	-0.7 (1.7)	32	0 (1.7)		100%	-0.7[-1.54,0.14]
Subtotal ***	**46**		**45**			**100%**	**-0.7[-1.54,0.14]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.63(P=0.1)							
Total ***	**46**		**45**			**100%**	**-0.7[-1.54,0.14]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.63(P=0.1)							



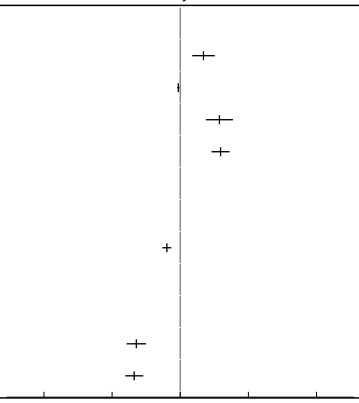
Analysis 1.37. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 37 Adverse events: 2. Movement disorders - b.vi. change scores (AIMS, high = bad).

Study or subgroup	AP combination N	AP combination Mean(SD)	AP monotherapy N	AP monotherapy Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.37.1 Other antipsychotic in both groups							
C +sulpiride 2013	31	-0.3 (1.9)	32	-0.4 (1.9)		100%	0.1[-0.84,1.04]
Subtotal ***	**31**		**32**			**100%**	**0.1[-0.84,1.04]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.21(P=0.83)							
Total ***	**31**		**32**			**100%**	**0.1[-0.84,1.04]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.21(P=0.83)							



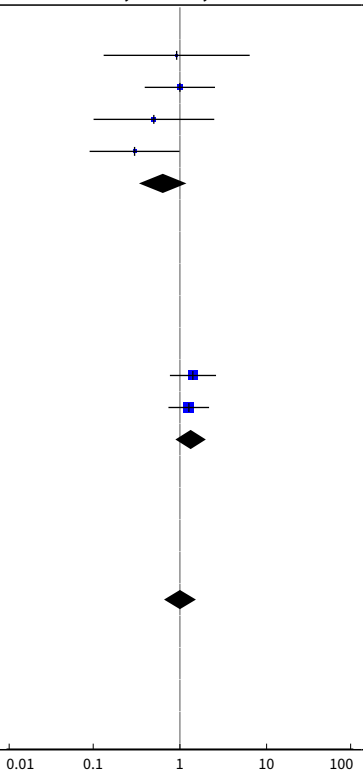
Analysis 1.38. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 38 Adverse events: 3. Endocrine - prolactin level (high = bad).

Study or subgroup	AP combination N	AP combination Mean(SD)	AP monotherapy N	AP monotherapy Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
1.38.1 clozapine in both groups						
B +risperidone 2010	20	41.7 (37.4)	24	7.6 (3.9)		34.1[17.63,50.57]
C +aripiprazole 2008	29	-2.3 (3.4)	32	0.5 (2.4)		-2.8[-4.29,-1.31]
C +risperidone 2005	16	59.3 (40.1)	14	1.8 (5.7)		57.5[37.63,77.37]
C +sulpiride 1997	16	77.9 (22.7)	12	18.7 (12.8)		59.19[45.92,72.46]
1.38.2 other atypical drugs in both groups						
C +aripiprazole 2007	31	51.8 (12.5)	30	71.4 (13.6)		-19.61[-26.17,-13.05]
1.38.3 typical drugs in both groups						
C +aripiprazole 2008b	40	22.8 (7.1)	40	87.2 (45.3)		-64.4[-78.61,-50.19]
C +aripiprazole 2009	30	-73.2 (27.2)	30	-5.7 (25.3)		-67.5[-80.79,-54.21]



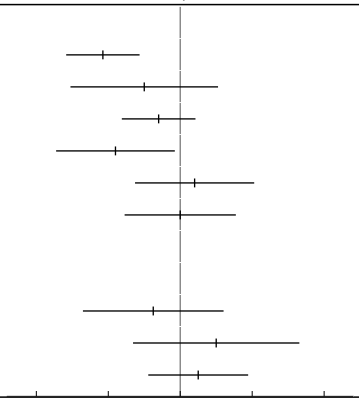
Analysis 1.39. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 39 Adverse events: 4. Metabolic - a. weight gain (binary).

Study or subgroup	AP combination n/N	AP monotherapy n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.39.1 clozapine in both groups					
B +aripiprazole 2008	2/108	2/99		4.47%	0.92[0.13,6.38]
C +risperidone 2006	7/34	7/34		16.06%	1[0.39,2.54]
C +sertindole 2006	2/25	4/25		6.36%	0.5[0.1,2.49]
C +sulpiride 2006	3/32	10/32		10.74%	0.3[0.09,0.99]
Subtotal (95% CI)	**199**	**190**		**37.64%**	**0.63[0.34,1.19]**
Total events: 14 (AP combination), 23 (AP monotherapy)					
Heterogeneity: Tau^2=0; Chi^2=2.67, df=3(P=0.44); I^2=0%					
Test for overall effect: Z=1.41(P=0.16)					
1.39.2 other atypical in both groups					
B +quet/risp 2009	23/168	15/155		28.91%	1.41[0.77,2.61]
C +sulpiride 2013	19/46	15/46		33.45%	1.27[0.74,2.17]
Subtotal (95% CI)	**214**	**201**		**62.36%**	**1.33[0.89,1.99]**
Total events: 42 (AP combination), 30 (AP monotherapy)					
Heterogeneity: Tau^2=0; Chi^2=0.07, df=1(P=0.79); I^2=0%					
Test for overall effect: Z=1.38(P=0.17)					
Total (95% CI)	**413**	**391**		**100%**	**1[0.66,1.53]**
Total events: 56 (AP combination), 53 (AP monotherapy)					
Heterogeneity: Tau^2=0.06; Chi^2=6.51, df=5(P=0.26); I^2=23.21%					
Test for overall effect: Z=0.01(P=0.99)					
Test for subgroup differences: Chi^2=3.72, df=1 (P=0.05), I^2=73.15%					



Analysis 1.40. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 40 Adverse events: 4. Metabolic - b. average weight gain (kg).

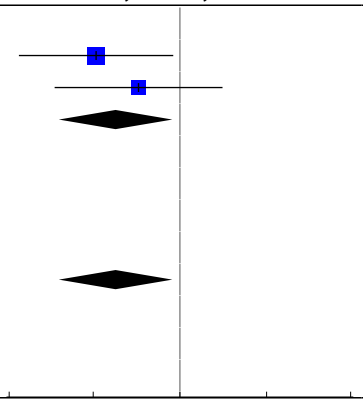
Study or subgroup	AP combination N	AP combination Mean(SD)	AP monotherapy N	AP monotherapy Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
1.40.1 clozapine in both groups						
B +aripiprazole 2008	108	-2.5 (3.7)	99	-0.4 (3.7)		-2.15[-3.17,-1.13]
B +risperidone 2010	24	0.1 (2.9)	26	1.1 (4.4)		-1[-3.05,1.05]
C +aripiprazole 2008	29	-1.2 (2.3)	32	-0.6 (1.7)		-0.6[-1.62,0.42]
C +aripiprazole 2013	16	-1.5 (2.3)	14	0.3 (2.3)		-1.8[-3.45,-0.15]
C +risperidone 2005	16	0.9 (2.2)	14	0.5 (2.4)		0.4[-1.26,2.06]
C +sertindole 2006	25	0.1 (2.7)	25	0.1 (2.9)		0[-1.55,1.55]
1.40.2 other atypical drugs in both groups						
C +olan/risp 2014	25	-0.3 (3.6)	26	0.4 (3.5)		-0.75[-2.7,1.2]
C +olanzapine 2012	13	2 (3.2)	13	1 (2.8)		1[-1.31,3.31]
C +sulpiride 2013	31	-0.8 (3)	32	-1.3 (2.6)		0.5[-0.89,1.89]



Favours AP combination — Favours AP monotherapy

Analysis 1.41. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 41 Adverse events: 5. Blood - a. decreased white cell counts (binary).

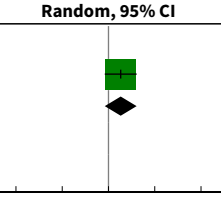
Study or subgroup	AP combination n/N	AP monotherapy n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.41.1 clozapine in both groups					
C +risperidone 2001	1/109	9/106		54.21%	0.11[0.01,0.84]
C +sulpiride 1999	1/50	3/50		45.79%	0.33[0.04,3.1]
Subtotal (95% CI)	**159**	**156**		**100%**	**0.18[0.04,0.82]**
Total events: 2 (AP combination), 12 (AP monotherapy)					
Heterogeneity: Tau^2=0; Chi^2=0.55, df=1(P=0.46); I^2=0%					
Test for overall effect: Z=2.22(P=0.03)					
Total (95% CI)	**159**	**156**		**100%**	**0.18[0.04,0.82]**
Total events: 2 (AP combination), 12 (AP monotherapy)					
Heterogeneity: Tau^2=0; Chi^2=0.55, df=1(P=0.46); I^2=0%					
Test for overall effect: Z=2.22(P=0.03)					



Favours AP combination — Favours AP monotherapy

Analysis 1.42. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 42 Adverse events: 5. Blood - b. average white cell counts ($10^{-3}/mm^3$).

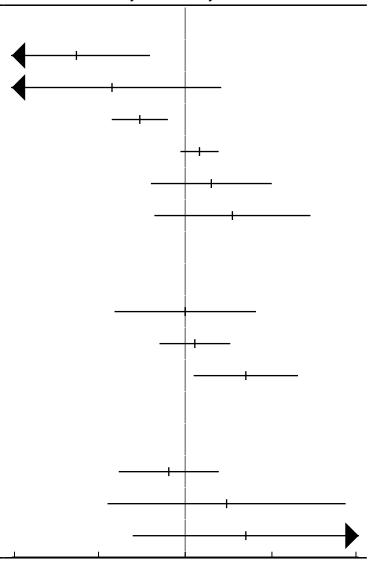
Study or subgroup	AP combination N	AP combination Mean(SD)	AP monotherapy N	AP monotherapy Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.42.1 clozapine in both groups							
C +risperidone 2006	30	7.5 (1.7)	31	6.9 (1.7)		100%	0.66[-0.2,1.52]
Subtotal ***	**30**		**31**			**100%**	**0.66[-0.2,1.52]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.5(P=0.13)							



Favours AP monotherapy — Favours AP combination

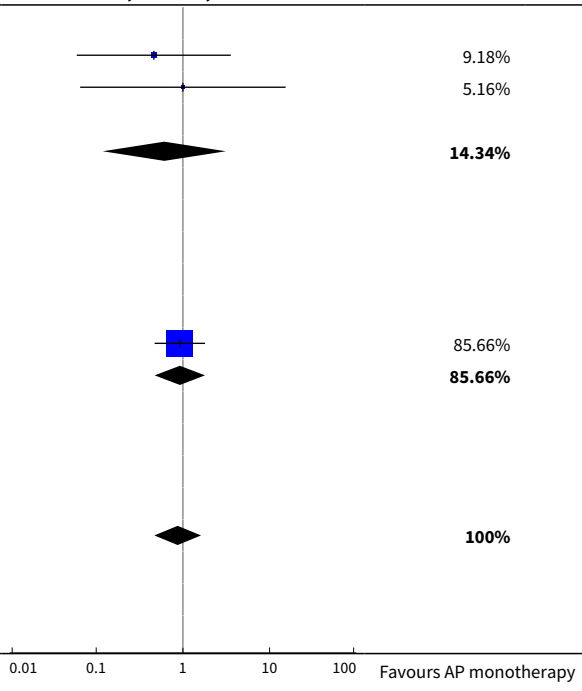
Analysis 1.43. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 43 Adverse events: 6. Central nervous system (CNS) - a. drowsiness.

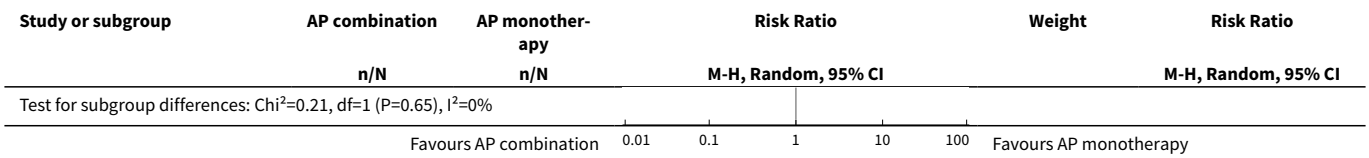
Study or subgroup	AP combination n/N	AP monotherapy n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
1.43.1 clozapine in both groups				
C +sertindole 2006	1/32	18/32		0.06[0.01,0.39]
C +risperidone 2001c	0/20	3/20		0.14[0.01,2.6]
C +risperidone 2001	8/109	26/106		0.3[0.14,0.63]
C +risperidone 2006	19/32	13/32		1.46[0.88,2.43]
C +sulpiride 1999b	4/25	2/25		2[0.4,9.95]
C +aripiprazole 2013	4/16	1/14		3.5[0.44,27.75]
1.43.2 other atypical in both groups				
C +clozapine 2013	2/25	2/25		1[0.15,6.55]
B +quet/risp 2009	10/169	7/153		1.29[0.5,3.31]
C +clozapine 2001	10/20	2/20		5[1.25,19.99]
1.43.3 typical drugs in both groups				
C +aripiprazole 2007b	3/26	5/28		0.65[0.17,2.44]
C +aripiprazole 2009	1/30	0/30		3[0.13,70.83]
C +aripiprazole 2008b	2/40	0/40		5[0.25,100.97]



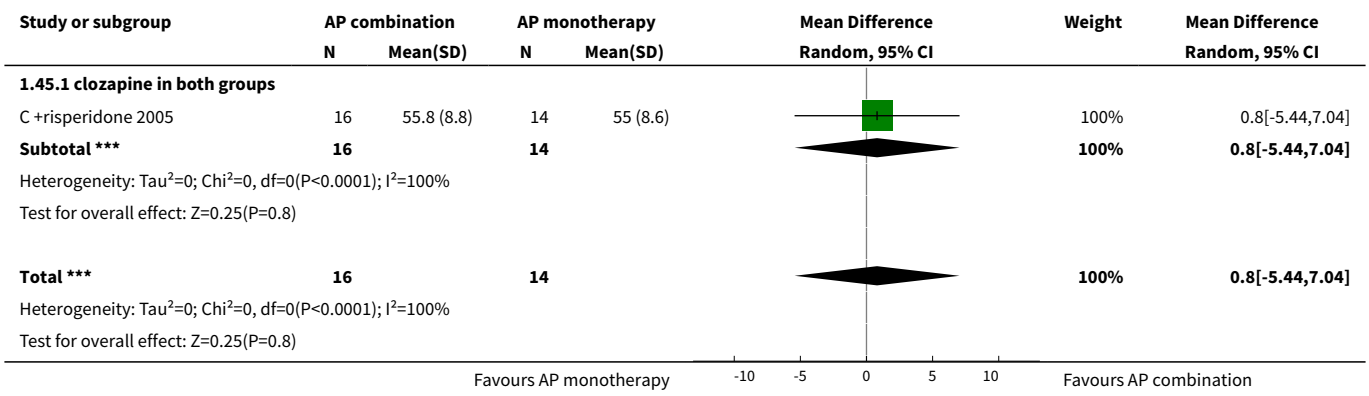
Analysis 1.44. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 44 Adverse events: 6. Central nervous system (CNS) - b. tremor.

Study or subgroup	AP combination n/N	AP monotherapy n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.44.1 clozapine in both groups					
C +amisulpride 2008	2/13	1/3		9.18%	0.46[0.06,3.57]
C +risperidone 2001c	1/32	1/32		5.16%	1[0.07,15.3]
C +sertindole 2006	0/25	0/25			Not estimable
Subtotal (95% CI)	**70**	**60**		**14.34%**	**0.61[0.12,3.13]**
Total events: 3 (AP combination), 2 (AP monotherapy)					
Heterogeneity: Tau²=0; Chi²=0.21, df=1(P=0.65); I²=0%					
Test for overall effect: Z=0.59(P=0.55)					
1.44.2 Other atypical in both groups					
C +sulpiride 2013	12/46	13/46		85.66%	0.92[0.47,1.8]
Subtotal (95% CI)	**46**	**46**		**85.66%**	**0.92[0.47,1.8]**
Total events: 12 (AP combination), 13 (AP monotherapy)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.23(P=0.81)					
Total (95% CI)	**116**	**106**		**100%**	**0.87[0.47,1.62]**
Total events: 15 (AP combination), 15 (AP monotherapy)					
Heterogeneity: Tau²=0; Chi²=0.41, df=2(P=0.81); I²=0%					
Test for overall effect: Z=0.44(P=0.66)					

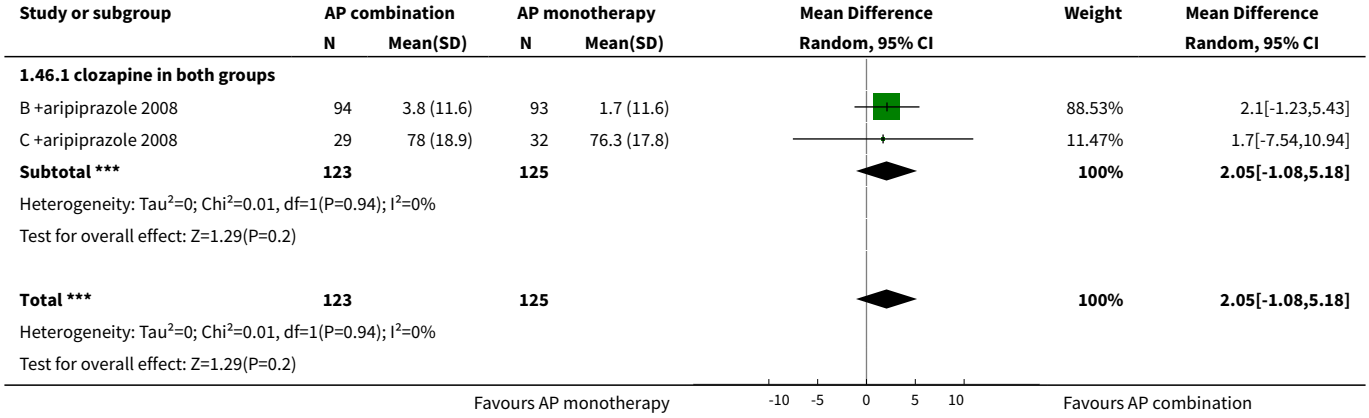




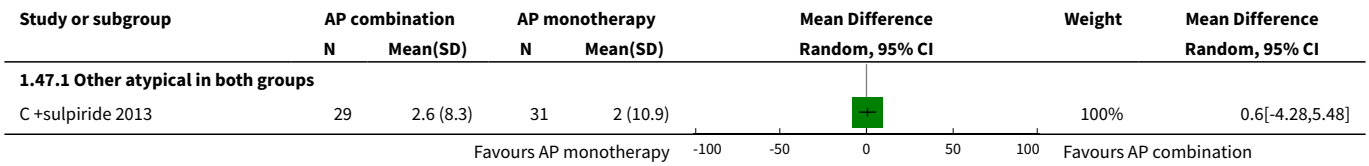
Analysis 1.45. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 45 Quality of life: 1a. Average score (QLS high=good).



Analysis 1.46. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 46 Quality of life: 1b. Average score (SWN, high=good).



Analysis 1.47. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 47 Quality of Life: 1c. Average score - Mental component summary (SF-36, high = good).



Study or subgroup	AP combination N	AP combination Mean(SD)	AP monotherapy N	AP monotherapy Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Subtotal ***	**29**		**31**			**100%**	**0.6[-4.28,5.48]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.24(P=0.81)							
Total ***	**29**		**31**			**100%**	**0.6[-4.28,5.48]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.24(P=0.81)							

Favours AP monotherapy -100 -50 0 50 100 Favours AP combination

Analysis 1.48. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 48 Quality of Life: 1d. Average score - Physical component summary (SF-36, high = good).

Study or subgroup	AP combination N	AP combination Mean(SD)	AP monotherapy N	AP monotherapy Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.48.1 Other atypical in both groups							
C +sulpiride 2013	29	0.4 (5.9)	31	2.1 (6)		100%	-1.7[-4.71,1.31]
Subtotal ***	**29**		**31**			**100%**	**-1.7[-4.71,1.31]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.11(P=0.27)							
Total ***	**29**		**31**			**100%**	**-1.7[-4.71,1.31]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.11(P=0.27)							

Favours AP monotherapy -100 -50 0 50 100 Favours AP combination

Analysis 1.49. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 49 SUBGROUP ANALYSIS Clinical Response: Not clinically improved - Patients enrolled in the studies.

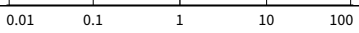
Study or subgroup	AP combination n/N	AP monotherapy n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.49.1 Chronic					
A +pimozide 1985	26/47	43/46		9.48%	0.59[0.45,0.77]
A +reserpine 1957	3/10	12/20		1.7%	0.5[0.18,1.38]
A +trifluoperazine 1964	9/27	34/50		4.32%	0.49[0.28,0.86]
B +quet/risp 2009	89/168	93/155		11.39%	0.88[0.73,1.07]
B +sulpiride 1996	3/31	7/32		1.15%	0.44[0.13,1.56]
C +clozapine 2001	1/20	0/20		0.2%	3[0.13,69.52]
C +CPZ 1973	2/15	12/31		0.99%	0.34[0.09,1.35]
C +risperidone 2001b	13/34	12/32		3.81%	1.02[0.55,1.89]
C +risperidone 2005	14/16	10/14		7.04%	1.23[0.84,1.79]
C +risperidone 2005b	13/20	18/20		7.56%	0.72[0.51,1.03]
C +risperidone 2006	28/34	25/34		9.81%	1.12[0.87,1.44]
C +risperidone 2007	9/11	12/13		8.27%	0.89[0.64,1.22]
C +sulpiride 1997	8/16	11/12		4.87%	0.55[0.32,0.92]
C +sulpiride 1999c	4/29	11/30		1.67%	0.38[0.14,1.05]
Subtotal (95% CI)	**478**	**509**		**72.25%**	**0.77[0.63,0.93]**

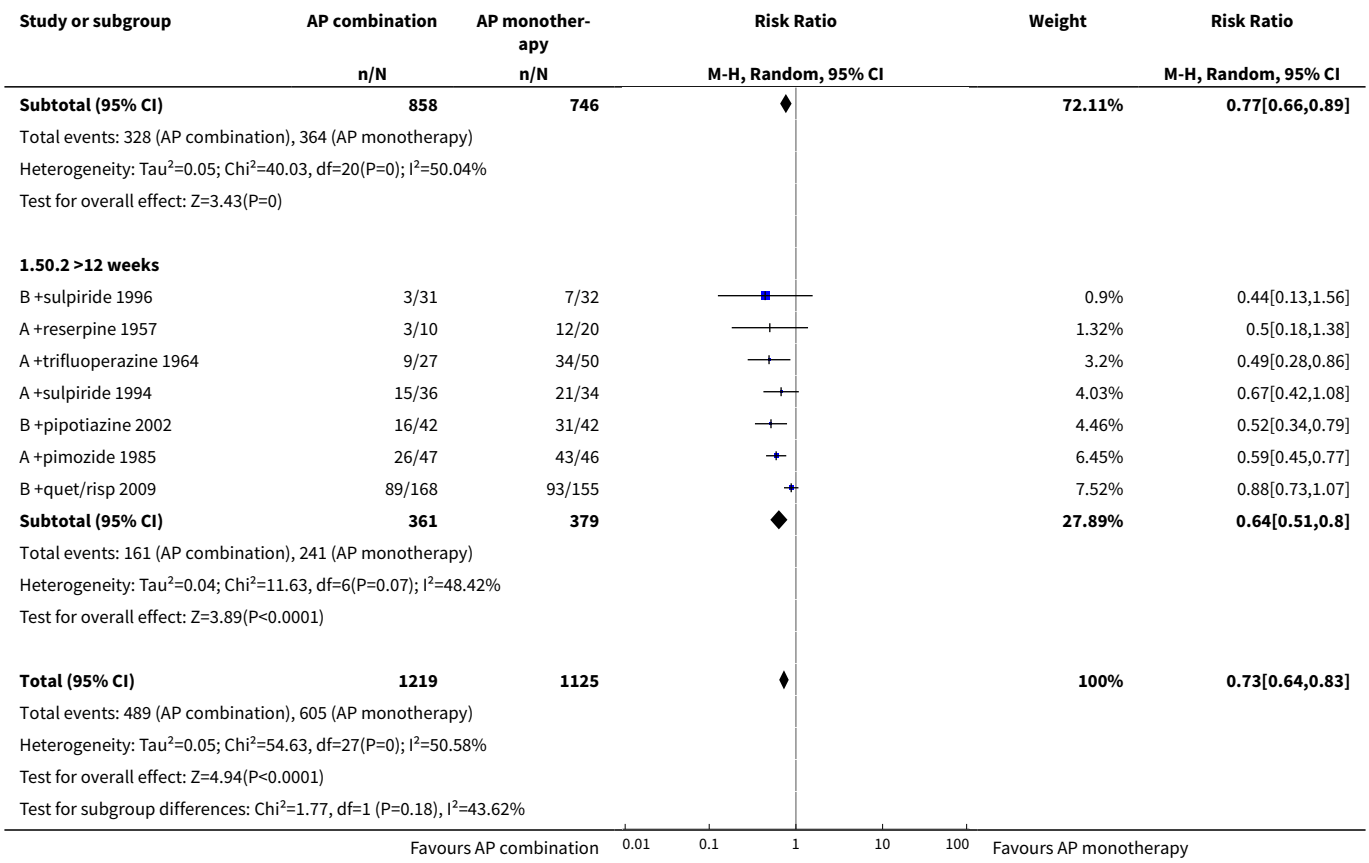
Favours AP combination 0.01 0.1 1 10 100 Favours monotherapy

Study or subgroup	AP combination	AP monotherapy	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Total events: 222 (AP combination), 300 (AP monotherapy)					
Heterogeneity: Tau²=0.06; Chi²=30.92, df=13(P=0); I²=57.96%					
Test for overall effect: Z=2.72(P=0.01)					
1.49.2 Acute					
C +haloperidol 2010	15/46	16/42		4.32%	0.86[0.49,1.51]
C +olan/risp 2014	16/25	22/26		7.91%	0.76[0.54,1.06]
C +olanzapine 2012	10/13	10/13		6.3%	1[0.66,1.52]
C +sulpiride 2013	30/46	33/46		9.23%	0.91[0.69,1.2]
Subtotal (95% CI)	**130**	**127**		**27.75%**	**0.87[0.73,1.05]**
Total events: 71 (AP combination), 81 (AP monotherapy)					
Heterogeneity: Tau²=0; Chi²=1.18, df=3(P=0.76); I²=0%					
Test for overall effect: Z=1.48(P=0.14)					
Total (95% CI)	**608**	**636**		**100%**	**0.81[0.7,0.93]**
Total events: 293 (AP combination), 381 (AP monotherapy)					
Heterogeneity: Tau²=0.04; Chi²=32.14, df=17(P=0.01); I²=47.1%					
Test for overall effect: Z=3.01(P=0)					
Test for subgroup differences: Chi²=0.91, df=1 (P=0.34), I²=0%					

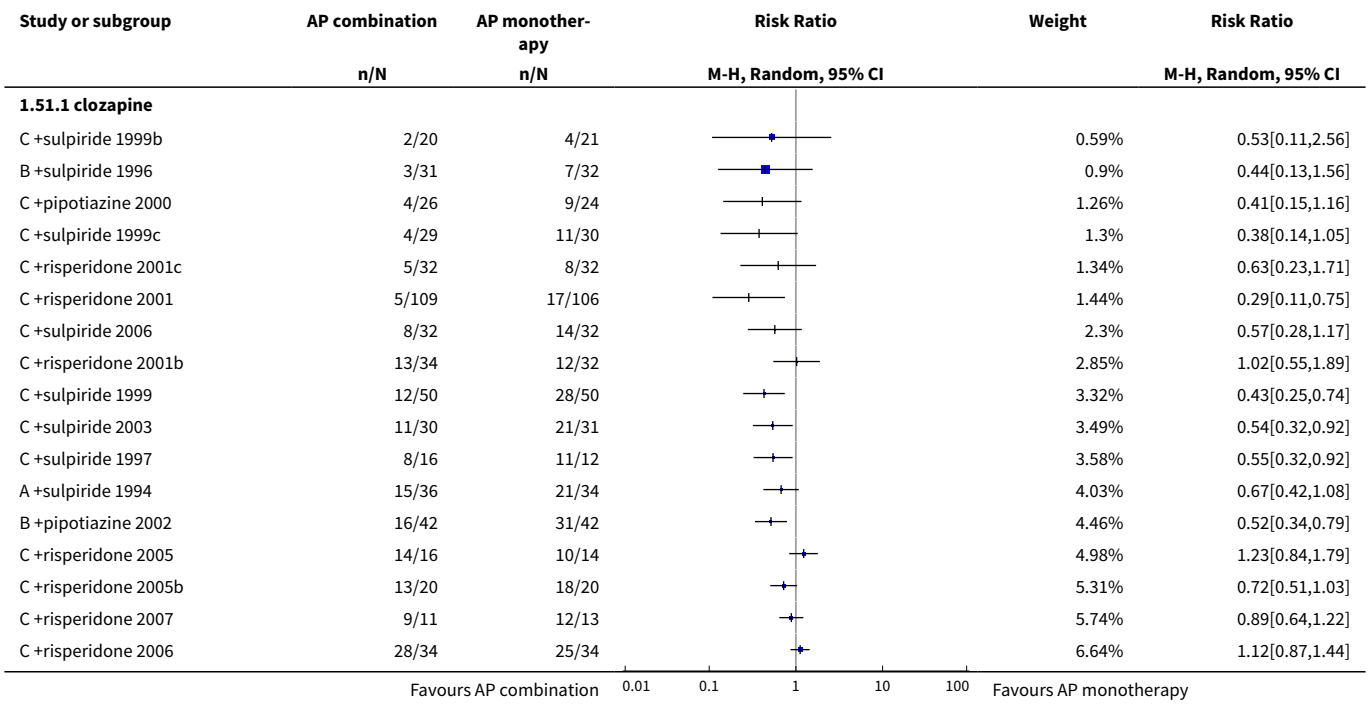
Analysis 1.50. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 50 SUBGROUP ANALYSIS Clinical Response: Not clinically improved - Treatment duration.

Study or subgroup	AP combination	AP monotherapy	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
1.50.1 ≤12 weeks					
C +clozapine 2001	1/20	0/20		0.16%	3[0.13,69.52]
C +sulpiride 1999b	2/20	4/21		0.59%	0.53[0.11,2.56]
C +CPZ 1973	2/15	12/31		0.78%	0.34[0.09,1.35]
C +pipotiazine 2000	4/26	9/24		1.26%	0.41[0.15,1.16]
C +sulpiride 1999c	4/29	11/30		1.3%	0.38[0.14,1.05]
C +risperidone 2001c	5/32	8/32		1.34%	0.63[0.23,1.71]
C +risperidone 2001	5/109	17/106		1.44%	0.29[0.11,0.75]
C +sulpiride 2006	8/32	14/32		2.3%	0.57[0.28,1.17]
C +risperidone 2001b	13/34	12/32		2.85%	1.02[0.55,1.89]
C +haloperidol 2010	15/46	16/42		3.2%	0.86[0.49,1.51]
C +sulpiride 1999	12/50	28/50		3.32%	0.43[0.25,0.74]
C +sulpiride 2003	11/30	21/31		3.49%	0.54[0.32,0.92]
C +sulpiride 1997	8/16	11/12		3.58%	0.55[0.32,0.92]
C +olanzapine 2012	10/13	10/13		4.51%	1[0.66,1.52]
C +risperidone 2005	14/16	10/14		4.98%	1.23[0.84,1.79]
C +risperidone 2005b	13/20	18/20		5.31%	0.72[0.51,1.03]
C +olan/risp 2014	16/25	22/26		5.52%	0.76[0.54,1.06]
C +risperidone 2007	9/11	12/13		5.74%	0.89[0.64,1.22]
C +sulpiride 2013	30/46	33/46		6.31%	0.91[0.69,1.2]
C +risperidone 2006	28/34	25/34		6.64%	1.12[0.87,1.44]
C +perphenazine 1976	118/234	71/117		7.5%	0.83[0.68,1.01]

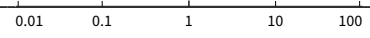




Analysis 1.51. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 51 SUBGROUP ANALYSIS Clinical Response: Not clinically improved - Use of clozapine in both groups.

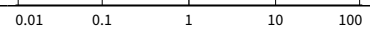


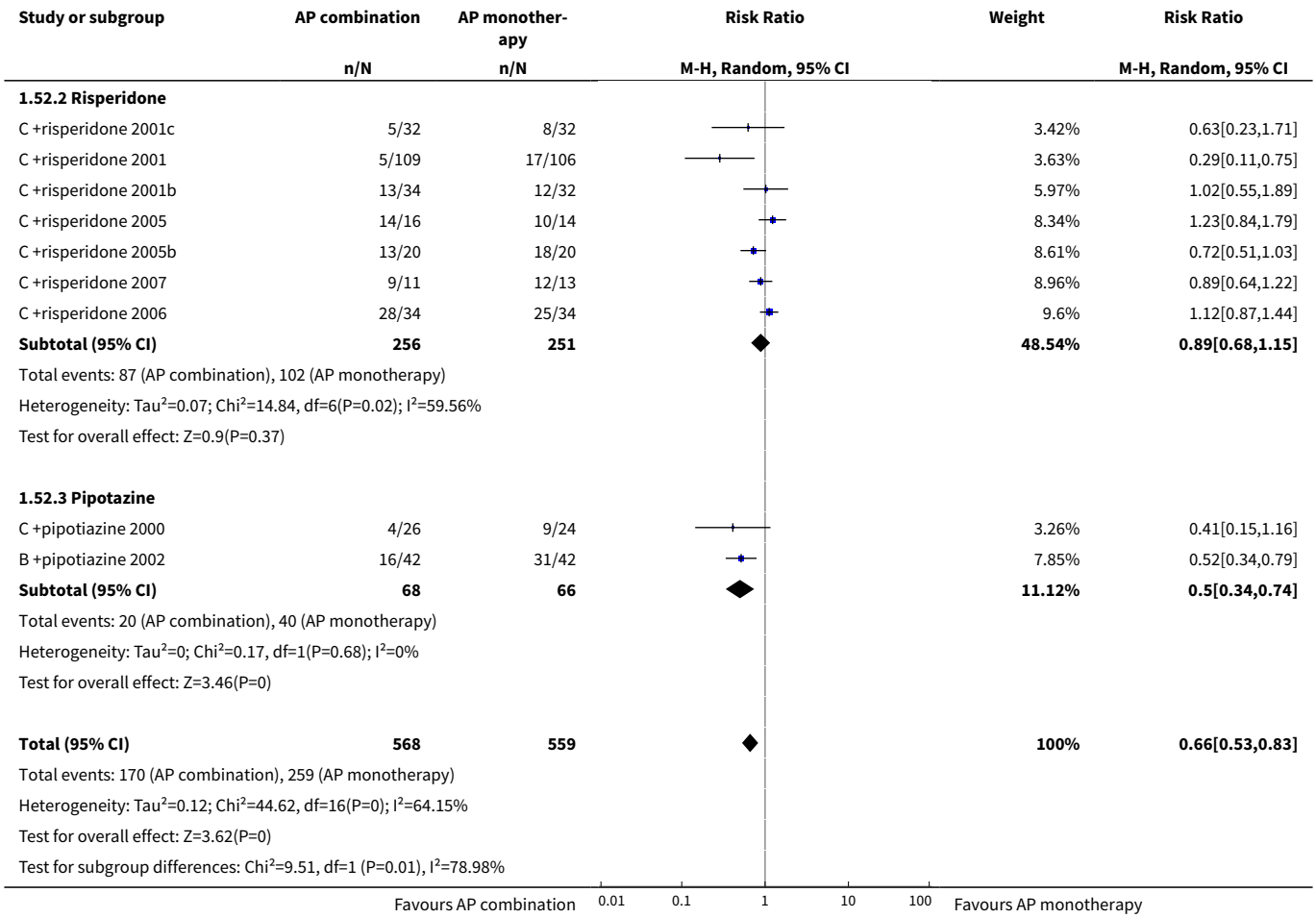
Study or subgroup	AP combination n/N	AP monotherapy n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Subtotal (95% CI)	**568**	**559**		**53.53%**	**0.66[0.53,0.83]**
Total events: 170 (AP combination), 259 (AP monotherapy)					
Heterogeneity: Tau²=0.12; Chi²=44.62, df=16(P=0); I²=64.15%					
Test for overall effect: Z=3.62(P=0)					
1.51.2 other antipsychotic					
C +clozapine 2001	1/20	0/20		0.16%	3[0.13,69.52]
C +CPZ 1973	2/15	12/31		0.78%	0.34[0.09,1.35]
A +reserpine 1957	3/10	12/20		1.32%	0.5[0.18,1.38]
C +haloperidol 2010	15/46	16/42		3.2%	0.86[0.49,1.51]
A +trifluoperazine 1964	9/27	34/50		3.2%	0.49[0.28,0.86]
C +olanzapine 2012	10/13	10/13		4.51%	1[0.66,1.52]
C +olan/risp 2014	16/25	22/26		5.52%	0.76[0.54,1.06]
C +sulpiride 2013	30/46	33/46		6.31%	0.91[0.69,1.2]
A +pimozide 1985	26/47	43/46		6.45%	0.59[0.45,0.77]
C +perphenazine 1976	118/234	71/117		7.5%	0.83[0.68,1.01]
B +quet/risp 2009	89/168	93/155		7.52%	0.88[0.73,1.07]
Subtotal (95% CI)	**651**	**566**		**46.47%**	**0.78[0.69,0.89]**
Total events: 319 (AP combination), 346 (AP monotherapy)					
Heterogeneity: Tau²=0.01; Chi²=14.01, df=10(P=0.17); I²=28.62%					
Test for overall effect: Z=3.61(P=0)					
Total (95% CI)	**1219**	**1125**		**100%**	**0.73[0.64,0.83]**
Total events: 489 (AP combination), 605 (AP monotherapy)					
Heterogeneity: Tau²=0.05; Chi²=54.63, df=27(P=0); I²=50.58%					
Test for overall effect: Z=4.94(P<0.0001)					
Test for subgroup differences: Chi²=1.66, df=1 (P=0.2), I²=39.58%					



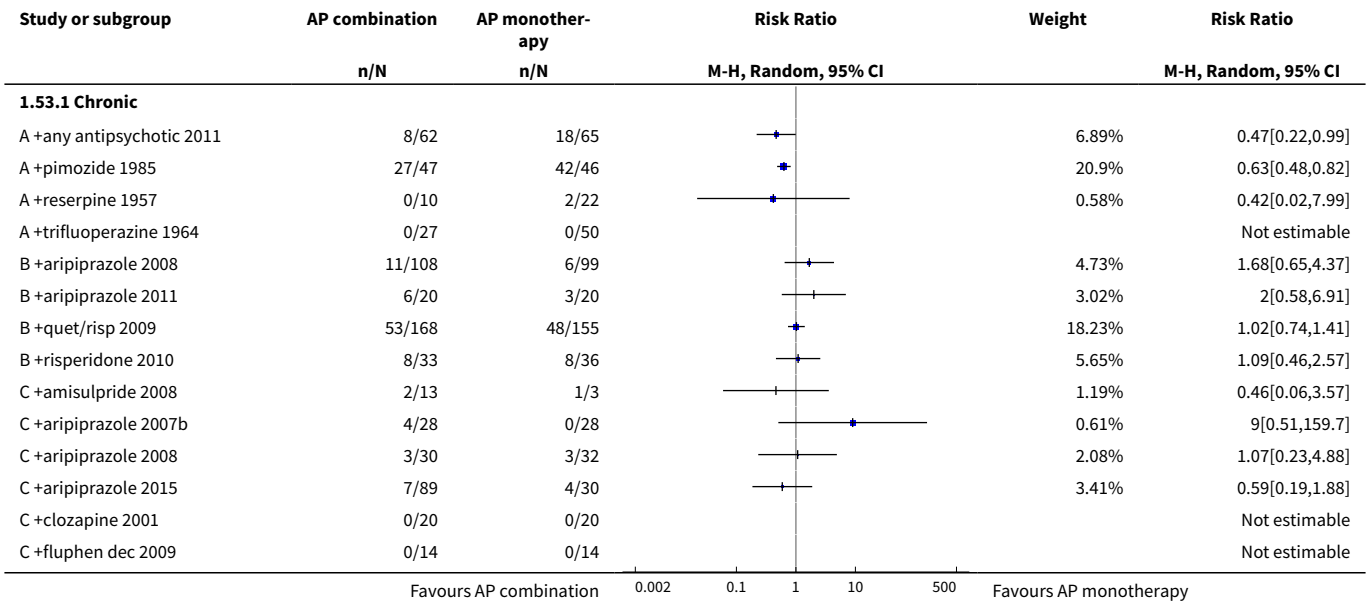
Analysis 1.52. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 52 SUBGROUP ANALYSIS Clinical Response: Not clinically improved - Drug added to clozapine.

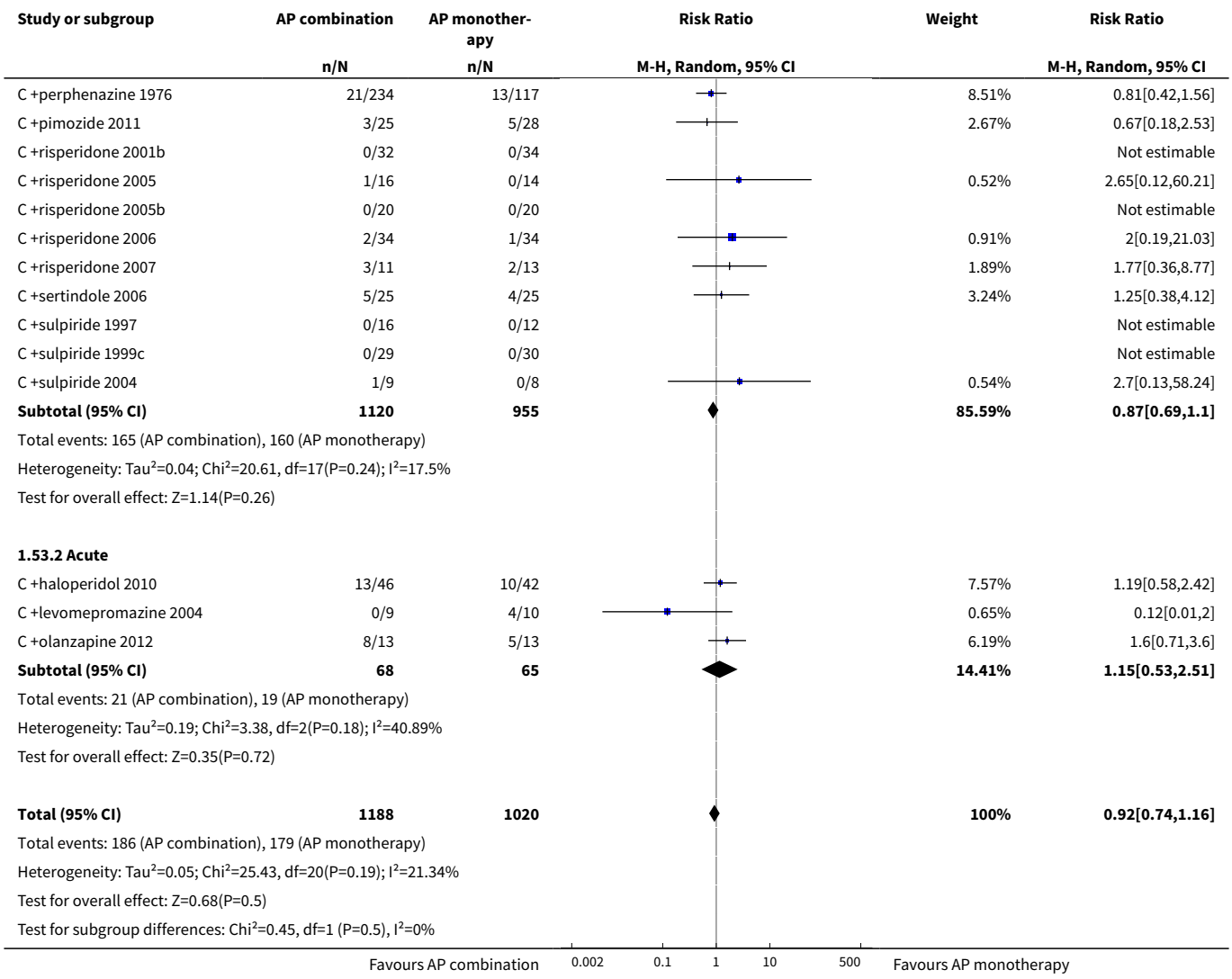
Study or subgroup	AP combination n/N	AP monotherapy n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.52.1 Sulpirirde					
C +sulpiride 1999b	2/20	4/21		1.69%	0.53[0.11,2.56]
B +sulpiride 1996	3/31	7/32		2.46%	0.44[0.13,1.56]
C +sulpiride 1999c	4/29	11/30		3.33%	0.38[0.14,1.05]
C +sulpiride 2006	8/32	14/32		5.16%	0.57[0.28,1.17]
C +sulpiride 1999	12/50	28/50		6.59%	0.43[0.25,0.74]
C +sulpiride 2003	11/30	21/31		6.8%	0.54[0.32,0.92]
C +sulpiride 1997	8/16	11/12		6.9%	0.55[0.32,0.92]
A +sulpiride 1994	15/36	21/34		7.41%	0.67[0.42,1.08]
Subtotal (95% CI)	**244**	**242**		**40.34%**	**0.54[0.43,0.68]**
Total events: 63 (AP combination), 117 (AP monotherapy)					
Heterogeneity: Tau²=0; Chi²=2.21, df=7(P=0.95); I²=0%					
Test for overall effect: Z=5.31(P<0.0001)					



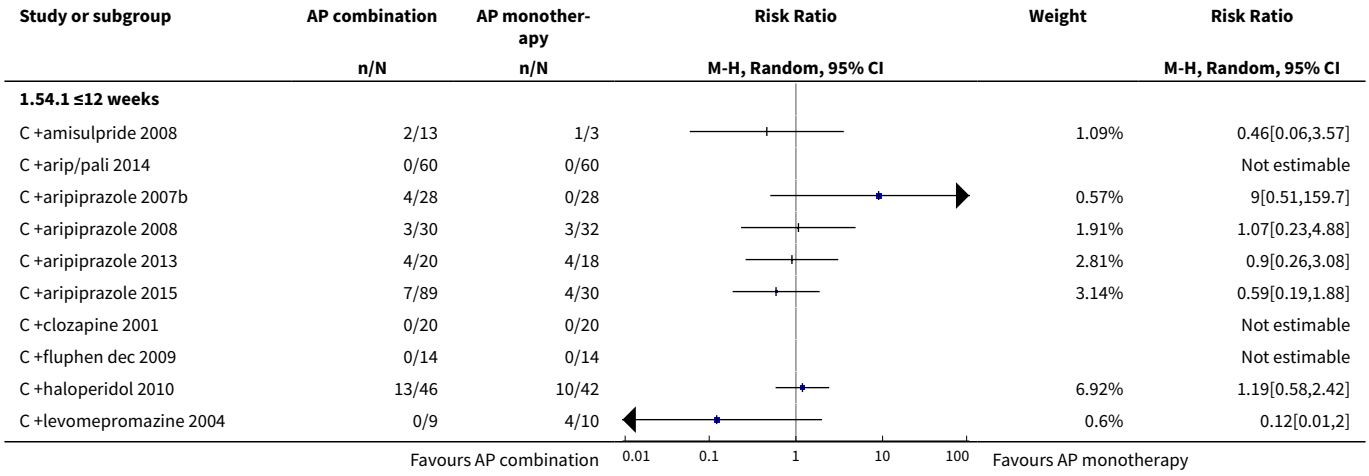


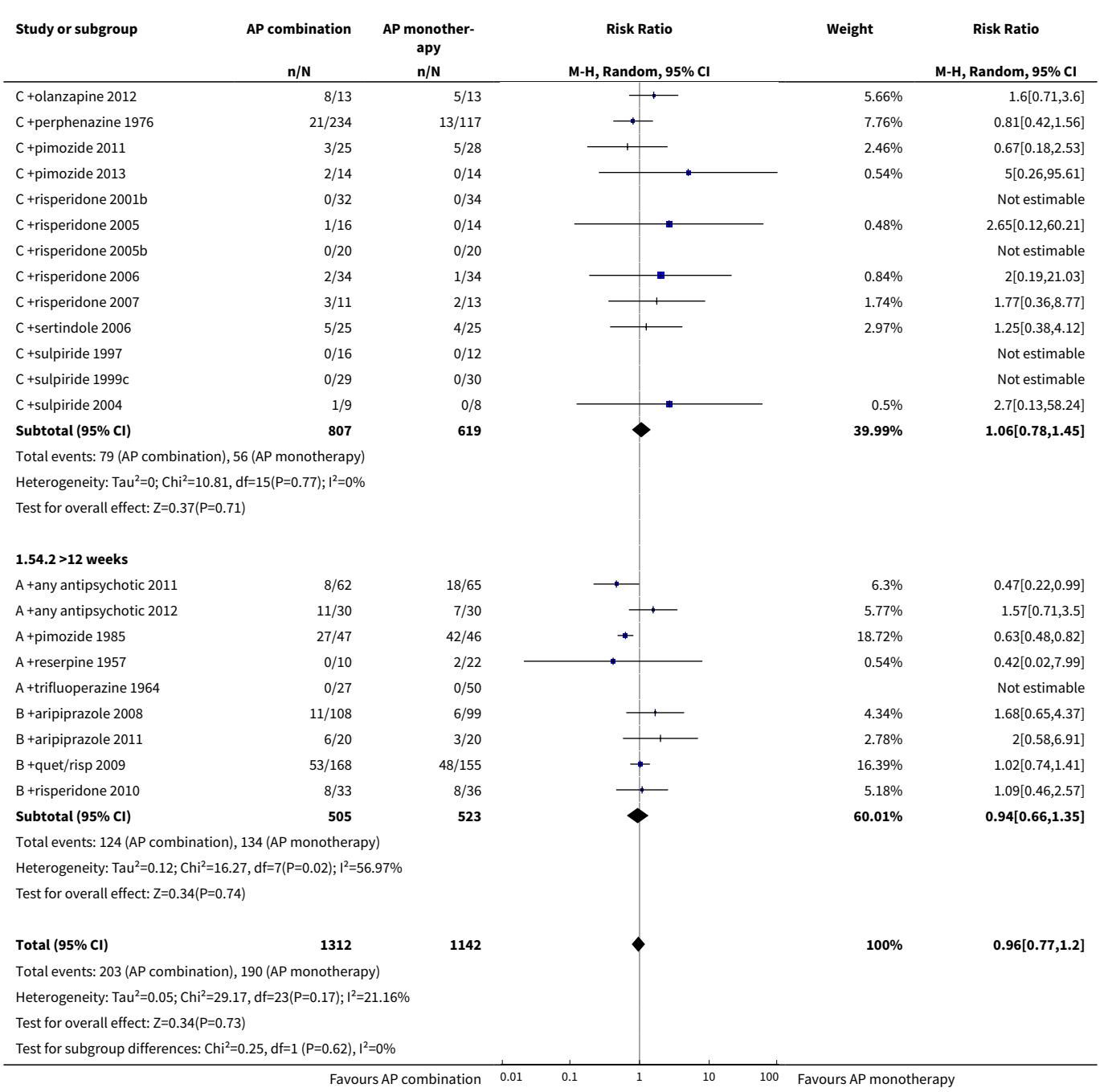
Analysis 1.53. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 53 SUBGROUP ANALYSIS Leaving the study early - Patients enrolled in the studies.



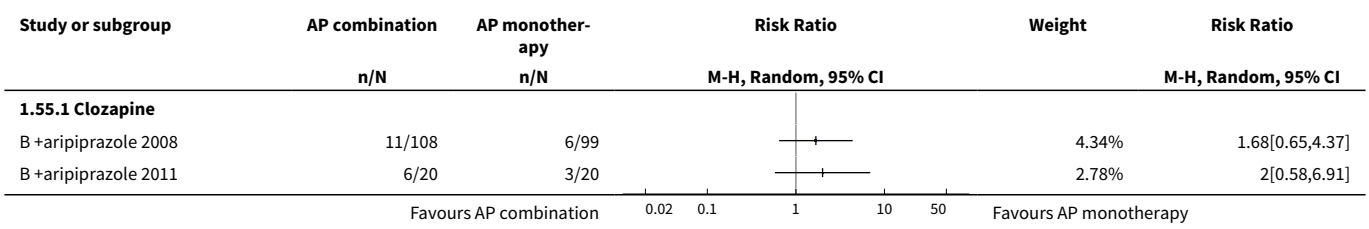


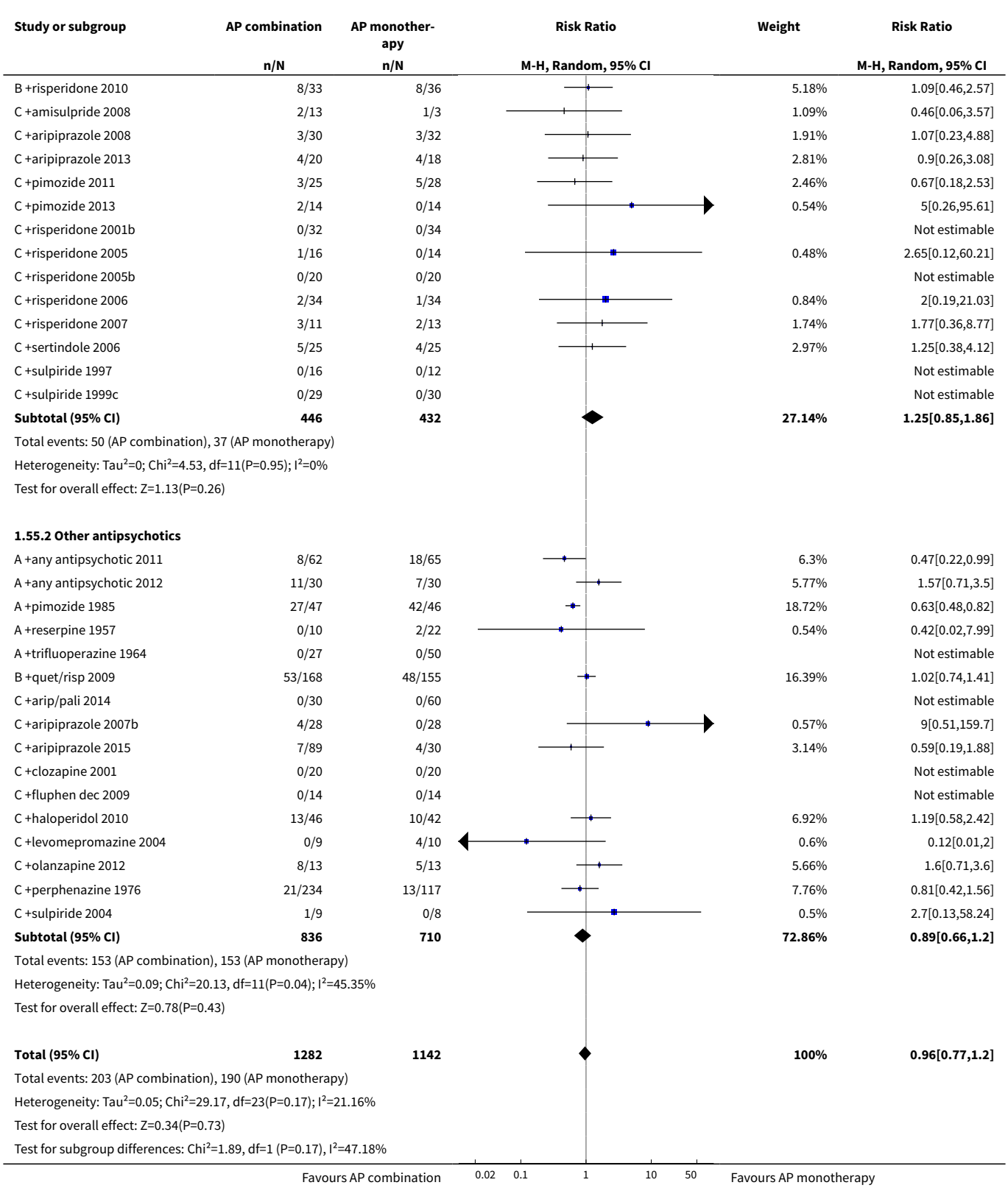
Analysis 1.54. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 54 SUBGROUP ANALYSIS Leaving the study early - Treatment duration.





Analysis 1.55. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 55 SUBGROUP ANALYSIS Leaving the study early - Use of clozapine in both groups.

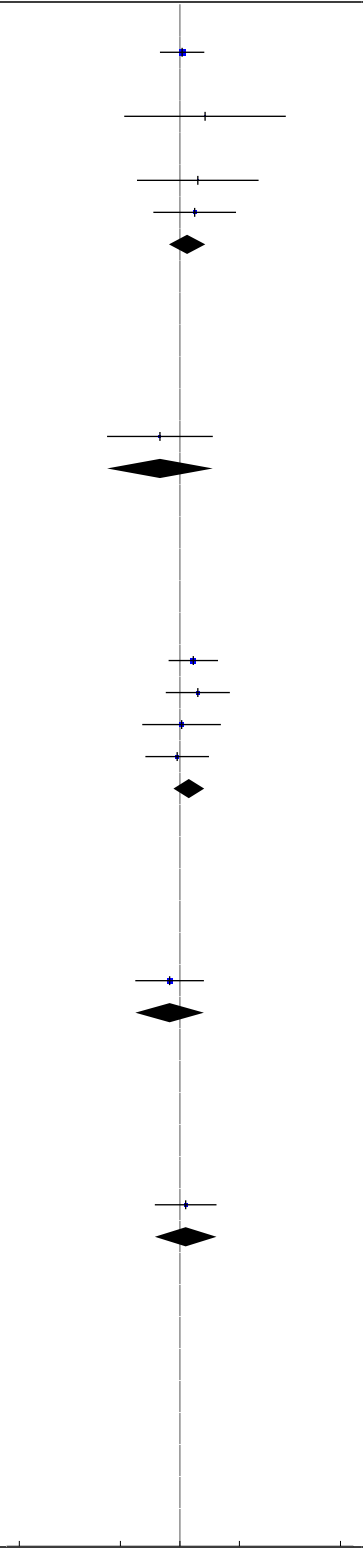




Study or subgroup	AP combination n/N	AP monotherapy n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
B +risperidone 2010	8/33	8/36		5.18%	1.09[0.46,2.57]
C +amisulpride 2008	2/13	1/3		1.09%	0.46[0.06,3.57]
C +aripiprazole 2008	3/30	3/32		1.91%	1.07[0.23,4.88]
C +aripiprazole 2013	4/20	4/18		2.81%	0.9[0.26,3.08]
C +pimozide 2011	3/25	5/28		2.46%	0.67[0.18,2.53]
C +pimozide 2013	2/14	0/14		0.54%	5[0.26,95.61]
C +risperidone 2001b	0/32	0/34			Not estimable
C +risperidone 2005	1/16	0/14		0.48%	2.65[0.12,60.21]
C +risperidone 2005b	0/20	0/20			Not estimable
C +risperidone 2006	2/34	1/34		0.84%	2[0.19,21.03]
C +risperidone 2007	3/11	2/13		1.74%	1.77[0.36,8.77]
C +sertindole 2006	5/25	4/25		2.97%	1.25[0.38,4.12]
C +sulpiride 1997	0/16	0/12			Not estimable
C +sulpiride 1999c	0/29	0/30			Not estimable
Subtotal (95% CI)	**446**	**432**		**27.14%**	**1.25[0.85,1.86]**
Total events: 50 (AP combination), 37 (AP monotherapy)					
Heterogeneity: Tau^2=0; Chi^2=4.53, df=11(P=0.95); I^2=0%					
Test for overall effect: Z=1.13(P=0.26)					
1.55.2 Other antipsychotics					
A +any antipsychotic 2011	8/62	18/65		6.3%	0.47[0.22,0.99]
A +any antipsychotic 2012	11/30	7/30		5.77%	1.57[0.71,3.5]
A +pimozide 1985	27/47	42/46		18.72%	0.63[0.48,0.82]
A +reserpine 1957	0/10	2/22		0.54%	0.42[0.02,7.99]
A +trifluoperazine 1964	0/27	0/50			Not estimable
B +quet/risp 2009	53/168	48/155		16.39%	1.02[0.74,1.41]
C +arip/pali 2014	0/30	0/60			Not estimable
C +aripiprazole 2007b	4/28	0/28		0.57%	9[0.51,159.7]
C +aripiprazole 2015	7/89	4/30		3.14%	0.59[0.19,1.88]
C +clozapine 2001	0/20	0/20			Not estimable
C +fluphen dec 2009	0/14	0/14			Not estimable
C +haloperidol 2010	13/46	10/42		6.92%	1.19[0.58,2.42]
C +levomepromazine 2004	0/9	4/10		0.6%	0.12[0.01,2]
C +olanzapine 2012	8/13	5/13		5.66%	1.6[0.71,3.6]
C +perphenazine 1976	21/234	13/117		7.76%	0.81[0.42,1.56]
C +sulpiride 2004	1/9	0/8		0.5%	2.7[0.13,58.24]
Subtotal (95% CI)	**836**	**710**		**72.86%**	**0.89[0.66,1.2]**
Total events: 153 (AP combination), 153 (AP monotherapy)					
Heterogeneity: Tau^2=0.09; Chi^2=20.13, df=11(P=0.04); I^2=45.35%					
Test for overall effect: Z=0.78(P=0.43)					
Total (95% CI)	**1282**	**1142**		**100%**	**0.96[0.77,1.2]**
Total events: 203 (AP combination), 190 (AP monotherapy)					
Heterogeneity: Tau^2=0.05; Chi^2=29.17, df=23(P=0.17); I^2=21.16%					
Test for overall effect: Z=0.34(P=0.73)					
Test for subgroup differences: Chi^2=1.89, df=1 (P=0.17), I^2=47.18%					

Analysis 1.56. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 56 SUBGROUP ANALYSIS Leaving the study early - Drug added to clozapine.

Study or subgroup	AP combination	AP monotherapy	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
1.56.1 Risperidone					
B +risperidone 2010	8/33	8/36		21.27%	1.09[0.46,2.57]
C +risperidone 2001b	0/32	0/34			Not estimable
C +risperidone 2005	1/16	0/14		1.61%	2.65[0.12,60.21]
C +risperidone 2005b	0/20	0/20			Not estimable
C +risperidone 2006	2/34	1/34		2.83%	2[0.19,21.03]
C +risperidone 2007	3/11	2/13		6.13%	1.77[0.36,8.77]
Subtotal (95% CI)	**146**	**151**		**31.84%**	**1.32[0.66,2.67]**
Total events: 14 (AP combination), 11 (AP monotherapy)					
Heterogeneity: Tau^2=0; Chi^2=0.64, df=3(P=0.89); I^2=0%					
Test for overall effect: Z=0.78(P=0.44)					
1.56.2 Amisulpiride					
C +amisulpride 2008	2/13	1/3		3.75%	0.46[0.06,3.57]
Subtotal (95% CI)	**13**	**3**		**3.75%**	**0.46[0.06,3.57]**
Total events: 2 (AP combination), 1 (AP monotherapy)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.74(P=0.46)					
1.56.3 Aripiprazole					
B +aripiprazole 2008	11/108	6/99		17.13%	1.68[0.65,4.37]
B +aripiprazole 2011	6/20	3/20		10.2%	2[0.58,6.91]
C +aripiprazole 2008	3/30	3/32		6.78%	1.07[0.23,4.88]
C +aripiprazole 2013	4/20	4/18		10.35%	0.9[0.26,3.08]
Subtotal (95% CI)	**178**	**169**		**44.47%**	**1.41[0.78,2.56]**
Total events: 24 (AP combination), 16 (AP monotherapy)					
Heterogeneity: Tau^2=0; Chi^2=1.08, df=3(P=0.78); I^2=0%					
Test for overall effect: Z=1.14(P=0.26)					
1.56.4 Pimozide					
C +pimozide 2011	3/25	5/28		8.92%	0.67[0.18,2.53]
Subtotal (95% CI)	**25**	**28**		**8.92%**	**0.67[0.18,2.53]**
Total events: 3 (AP combination), 5 (AP monotherapy)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.59(P=0.56)					
1.56.5 Sertindole					
C +sertindole 2006	5/25	4/25		11.03%	1.25[0.38,4.12]
Subtotal (95% CI)	**25**	**25**		**11.03%**	**1.25[0.38,4.12]**
Total events: 5 (AP combination), 4 (AP monotherapy)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.37(P=0.71)					
1.56.6 Sulpiride					
C +sulpiride 1997	0/16	0/12			Not estimable
C +sulpiride 1999c	0/29	0/30			Not estimable
Subtotal (95% CI)	**45**	**42**			**Not estimable**
Total events: 0 (AP combination), 0 (AP monotherapy)					



Study or subgroup	AP combination	AP monotherapy	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**432**	**418**		**100%**	**1.22[0.82,1.82]**
Total events: 48 (AP combination), 37 (AP monotherapy)					
Heterogeneity: Tau^2=0; Chi^2=3.65, df=10(P=0.96); I^2=0%					
Test for overall effect: Z=1(P=0.32)					
Test for subgroup differences: Chi^2=1.93, df=1 (P=0.75), I^2=0%					

Favours AP combination 0.002 0.1 1 10 500 Favours AP monotherapy

Analysis 1.57. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 57 SENSITIVITY ANALYSIS Clinical Response: Not clinically improved - Randomisation.

Study or subgroup	AP combination	AP monotherapy	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
1.57.1 Low / unclear risk of bias					
A +pimozide 1985	26/47	43/46		6.45%	0.59[0.45,0.77]
A +reserpine 1957	3/10	12/20		1.32%	0.5[0.18,1.38]
A +sulpiride 1994	15/36	21/34		4.03%	0.67[0.42,1.08]
A +trifluoperazine 1964	9/27	34/50		3.2%	0.49[0.28,0.86]
B +pipotiazine 2002	16/42	31/42		4.46%	0.52[0.34,0.79]
B +quet/risp 2009	89/168	93/155		7.52%	0.88[0.73,1.07]
C +clozapine 2001	1/20	0/20		0.16%	3[0.13,69.52]
C +CPZ 1973	2/15	12/31		0.78%	0.34[0.09,1.35]
C +haloperidol 2010	15/46	16/42		3.2%	0.86[0.49,1.51]
C +olan/risp 2014	16/25	22/26		5.52%	0.76[0.54,1.06]
C +olanzapine 2012	10/13	10/13		4.51%	1[0.66,1.52]
C +perphenazine 1976	118/234	71/117		7.5%	0.83[0.68,1.01]
C +pipotiazine 2000	4/26	9/24		1.26%	0.41[0.15,1.16]
C +risperidone 2001	5/109	17/106		1.44%	0.29[0.11,0.75]
C +risperidone 2001b	13/34	12/32		2.85%	1.02[0.55,1.89]
C +risperidone 2001c	5/32	8/32		1.34%	0.63[0.23,1.71]
C +risperidone 2005	14/16	10/14		4.98%	1.23[0.84,1.79]
C +risperidone 2005b	13/20	18/20		5.31%	0.72[0.51,1.03]
C +risperidone 2006	28/34	25/34		6.64%	1.12[0.87,1.44]
C +risperidone 2007	9/11	12/13		5.74%	0.89[0.64,1.22]
C +sulpiride 1997	8/16	11/12		3.58%	0.55[0.32,0.92]
C +sulpiride 1999c	4/29	11/30		1.3%	0.38[0.14,1.05]
C +sulpiride 2003	11/30	21/31		3.49%	0.54[0.32,0.92]
C +sulpiride 2006	8/32	14/32		2.3%	0.57[0.28,1.17]
C +sulpiride 2013	30/46	33/46		6.31%	0.91[0.69,1.2]
Subtotal (95% CI)	**1118**	**1022**		**95.19%**	**0.75[0.66,0.85]**
Total events: 472 (AP combination), 566 (AP monotherapy)					
Heterogeneity: Tau^2=0.04; Chi^2=47.64, df=24(P=0); I^2=49.63%					
Test for overall effect: Z=4.52(P<0.0001)					
1.57.2 High					
B +sulpiride 1996	3/31	7/32		0.9%	0.44[0.13,1.56]

Favours AP combination 0.01 0.1 1 10 100 Favours AP monotherapy

Study or subgroup	AP combination	AP monotherapy	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
C +sulpiride 1999	12/50	28/50		3.32%	0.43[0.25,0.74]
C +sulpiride 1999b	2/20	4/21		0.59%	0.53[0.11,2.56]
Subtotal (95% CI)	**101**	**103**		**4.81%**	**0.44[0.27,0.71]**
Total events: 17 (AP combination), 39 (AP monotherapy)					
Heterogeneity: Tau^2=0; Chi^2=0.06, df=2(P=0.97); I^2=0%					
Test for overall effect: Z=3.36(P=0)					
Total (95% CI)	**1219**	**1125**		**100%**	**0.73[0.64,0.83]**
Total events: 489 (AP combination), 605 (AP monotherapy)					
Heterogeneity: Tau^2=0.05; Chi^2=54.63, df=27(P=0); I^2=50.58%					
Test for overall effect: Z=4.94(P<0.0001)					
Test for subgroup differences: Chi^2=4.48, df=1 (P=0.03), I^2=77.68%					

Favours AP combination 0.01 0.1 1 10 100 Favours AP monotherapy

Analysis 1.58. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 58 SENSITIVITY ANALYSIS Clinical Response: Not clinically improved - Double blind.

Study or subgroup	AP combination	AP monotherapy	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
1.58.1 Low / unclear					
A +pimozide 1985	26/47	43/46		6.45%	0.59[0.45,0.77]
A +reserpine 1957	3/10	12/20		1.32%	0.5[0.18,1.38]
A +trifluoperazine 1964	9/27	34/50		3.2%	0.49[0.28,0.86]
B +pipotiazine 2002	16/42	31/42		4.46%	0.52[0.34,0.79]
B +quet/risp 2009	89/168	93/155		7.52%	0.88[0.73,1.07]
B +sulpiride 1996	3/31	7/32		0.9%	0.44[0.13,1.56]
C +clozapine 2001	1/20	0/20		0.16%	3[0.13,69.52]
C +CPZ 1973	2/15	12/31		0.78%	0.34[0.09,1.35]
C +haloperidol 2010	15/46	16/42		3.2%	0.86[0.49,1.51]
C +perphenazine 1976	118/234	71/117		7.5%	0.83[0.68,1.01]
C +pipotiazine 2000	4/26	9/24		1.26%	0.41[0.15,1.16]
C +risperidone 2001	5/109	17/106		1.44%	0.29[0.11,0.75]
C +risperidone 2001b	13/34	12/32		2.85%	1.02[0.55,1.89]
C +risperidone 2001c	5/32	8/32		1.34%	0.63[0.23,1.71]
C +risperidone 2005	14/16	10/14		4.98%	1.23[0.84,1.79]
C +risperidone 2005b	13/20	18/20		5.31%	0.72[0.51,1.03]
C +risperidone 2006	28/34	25/34		6.64%	1.12[0.87,1.44]
C +risperidone 2007	9/11	12/13		5.74%	0.89[0.64,1.22]
C +sulpiride 1997	8/16	11/12		3.58%	0.55[0.32,0.92]
C +sulpiride 1999	12/50	28/50		3.32%	0.43[0.25,0.74]
C +sulpiride 1999b	2/20	4/21		0.59%	0.53[0.11,2.56]
C +sulpiride 1999c	4/29	11/30		1.3%	0.38[0.14,1.05]
C +sulpiride 2003	11/30	21/31		3.49%	0.54[0.32,0.92]
C +sulpiride 2006	8/32	14/32		2.3%	0.57[0.28,1.17]
C +sulpiride 2013	30/46	33/46		6.31%	0.91[0.69,1.2]
Subtotal (95% CI)	**1145**	**1052**		**85.94%**	**0.71[0.62,0.82]**
Total events: 448 (AP combination), 552 (AP monotherapy)					
Heterogeneity: Tau^2=0.05; Chi^2=52.79, df=24(P=0); I^2=54.53%					

Favours AP combination 0.01 0.1 1 10 100 Favours AP monotherapy

Study or subgroup	AP combination n/N	AP monotherapy n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=4.69(P<0.0001)					
1.58.2 High					
A +sulpiride 1994	15/36	21/34		4.03%	0.67[0.42,1.08]
C +olan/risp 2014	16/25	22/26		5.52%	0.76[0.54,1.06]
C +olanzapine 2012	10/13	10/13		4.51%	1[0.66,1.52]
Subtotal (95% CI)	**74**	**73**		**14.06%**	**0.8[0.64,1.01]**
Total events: 41 (AP combination), 53 (AP monotherapy)					
Heterogeneity: Tau²=0; Chi²=1.8, df=2(P=0.41); I²=0%					
Test for overall effect: Z=1.91(P=0.06)					
Total (95% CI)	**1219**	**1125**		**100%**	**0.73[0.64,0.83]**
Total events: 489 (AP combination), 605 (AP monotherapy)					
Heterogeneity: Tau²=0.05; Chi²=54.63, df=27(P=0); I²=50.58%					
Test for overall effect: Z=4.94(P<0.0001)					
Test for subgroup differences: Chi²=0.72, df=1 (P=0.4), I²=0%					

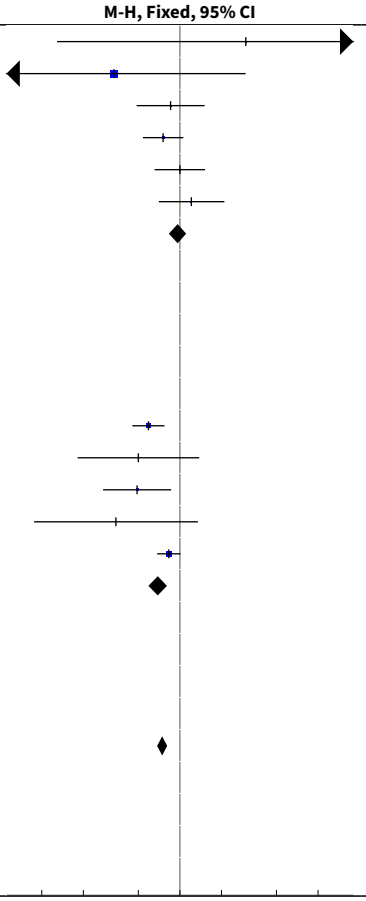
Favours AP combination — Favours AP monotherapy

Analysis 1.59. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 59 SENSITIVITY ANALYSIS Clinical response: 1. No clinically important response - not improved - Fixed effect.

Study or subgroup	AP combination n/N	AP monotherapy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.59.1 clozapine in both groups					
A +sulpiride 1994	15/36	21/34		3.59%	0.67[0.42,1.08]
B +pipotiazine 2002	16/42	31/42		5.15%	0.52[0.34,0.79]
B +sulpiride 1996	3/31	7/32		1.14%	0.44[0.13,1.56]
C +pipotiazine 2000	4/26	9/24		1.56%	0.41[0.15,1.16]
C +risperidone 2001	5/109	17/106		2.86%	0.29[0.11,0.75]
C +risperidone 2001b	13/34	12/32		2.05%	1.02[0.55,1.89]
C +risperidone 2001c	5/32	8/32		1.33%	0.63[0.23,1.71]
C +risperidone 2005	14/16	10/14		1.77%	1.23[0.84,1.79]
C +risperidone 2005b	13/20	18/20		2.99%	0.72[0.51,1.03]
C +risperidone 2006	28/34	25/34		4.16%	1.12[0.87,1.44]
C +risperidone 2007	9/11	12/13		1.83%	0.89[0.64,1.22]
C +sulpiride 1997	8/16	11/12		2.09%	0.55[0.32,0.92]
C +sulpiride 1999	12/50	28/50		4.65%	0.43[0.25,0.74]
C +sulpiride 1999b	2/20	4/21		0.65%	0.53[0.11,2.56]
C +sulpiride 1999c	4/29	11/30		1.8%	0.38[0.14,1.05]
C +sulpiride 2003	11/30	21/31		3.43%	0.54[0.32,0.92]
C +sulpiride 2006	8/32	14/32		2.33%	0.57[0.28,1.17]
Subtotal (95% CI)	**568**	**559**		**43.39%**	**0.64[0.56,0.74]**
Total events: 170 (AP combination), 259 (AP monotherapy)					
Heterogeneity: Tau²=0; Chi²=44.62, df=16(P=0); I²=64.15%					
Test for overall effect: Z=6.29(P<0.0001)					
1.59.2 other atypical in both groups					
B +quet/risp 2009	99/168	92/155		15.91%	0.99[0.83,1.19]

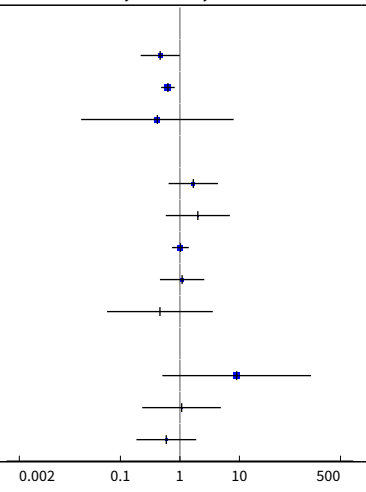
Favours AP combination — Favours AP monotherapy

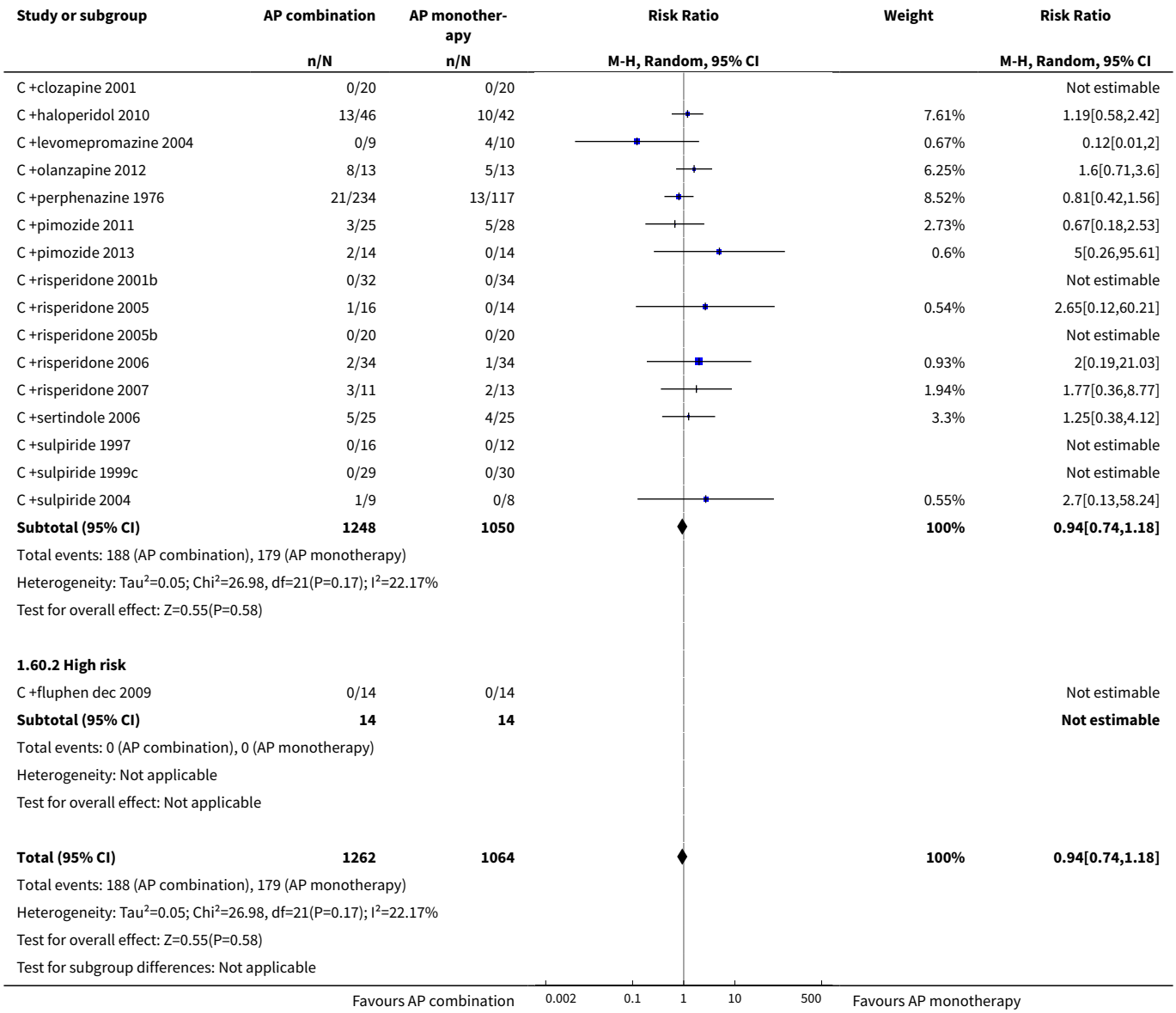
Study or subgroup	AP combination n/N	AP monotherapy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
C +clozapine 2001	1/20	0/20		0.08%	3[0.13,69.52]
C +clozapine 2013	1/25	3/25		0.5%	0.33[0.04,2.99]
C +haloperidol 2010	15/46	16/42		2.78%	0.86[0.49,1.51]
C +olan/risp 2014	16/25	22/26		3.58%	0.76[0.54,1.06]
C +olanzapine 2012	10/13	10/13		1.66%	1[0.66,1.52]
C +sulpiride 2013	19/49	15/47		2.54%	1.21[0.7,2.1]
Subtotal (95% CI)	**346**	**328**		**27.06%**	**0.96[0.83,1.11]**
Total events: 161 (AP combination), 158 (AP monotherapy)					
Heterogeneity: Tau²=0; Chi²=4.38, df=6(P=0.63); I²=0%					
Test for overall effect: Z=0.51(P=0.61)					
1.59.3 typical drugs in both groups					
A +pimozide 1985	26/47	43/46		7.22%	0.59[0.45,0.77]
A +reserpine 1957	3/10	12/20		1.33%	0.5[0.18,1.38]
A +trifluoperazine 1964	9/27	34/50		3.96%	0.49[0.28,0.86]
C +CPZ 1973	2/15	12/31		1.3%	0.34[0.09,1.35]
C +perphenazine 1976	118/234	71/117		15.73%	0.83[0.68,1.01]
Subtotal (95% CI)	**333**	**264**		**29.55%**	**0.69[0.59,0.81]**
Total events: 158 (AP combination), 172 (AP monotherapy)					
Heterogeneity: Tau²=0; Chi²=7.59, df=4(P=0.11); I²=47.3%					
Test for overall effect: Z=4.7(P<0.0001)					
Total (95% CI)	**1247**	**1151**		**100%**	**0.74[0.68,0.81]**
Total events: 489 (AP combination), 589 (AP monotherapy)					
Heterogeneity: Tau²=0; Chi²=60.79, df=28(P=0); I²=53.94%					
Test for overall effect: Z=6.93(P<0.0001)					
Test for subgroup differences: Chi²=17.19, df=1 (P=0), I²=88.37%					



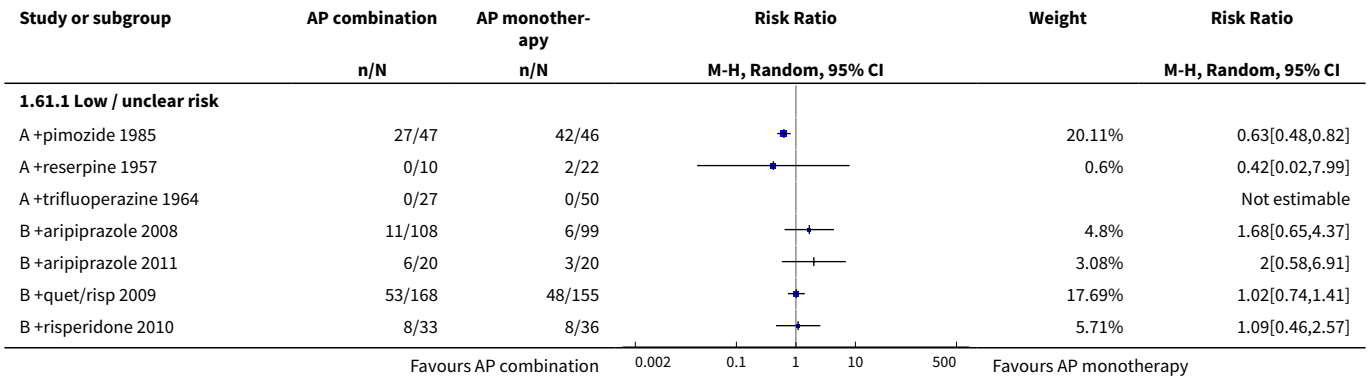
Analysis 1.60. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 60 SENSITIVITY ANALYSIS Leaving the study early - Randomisation.

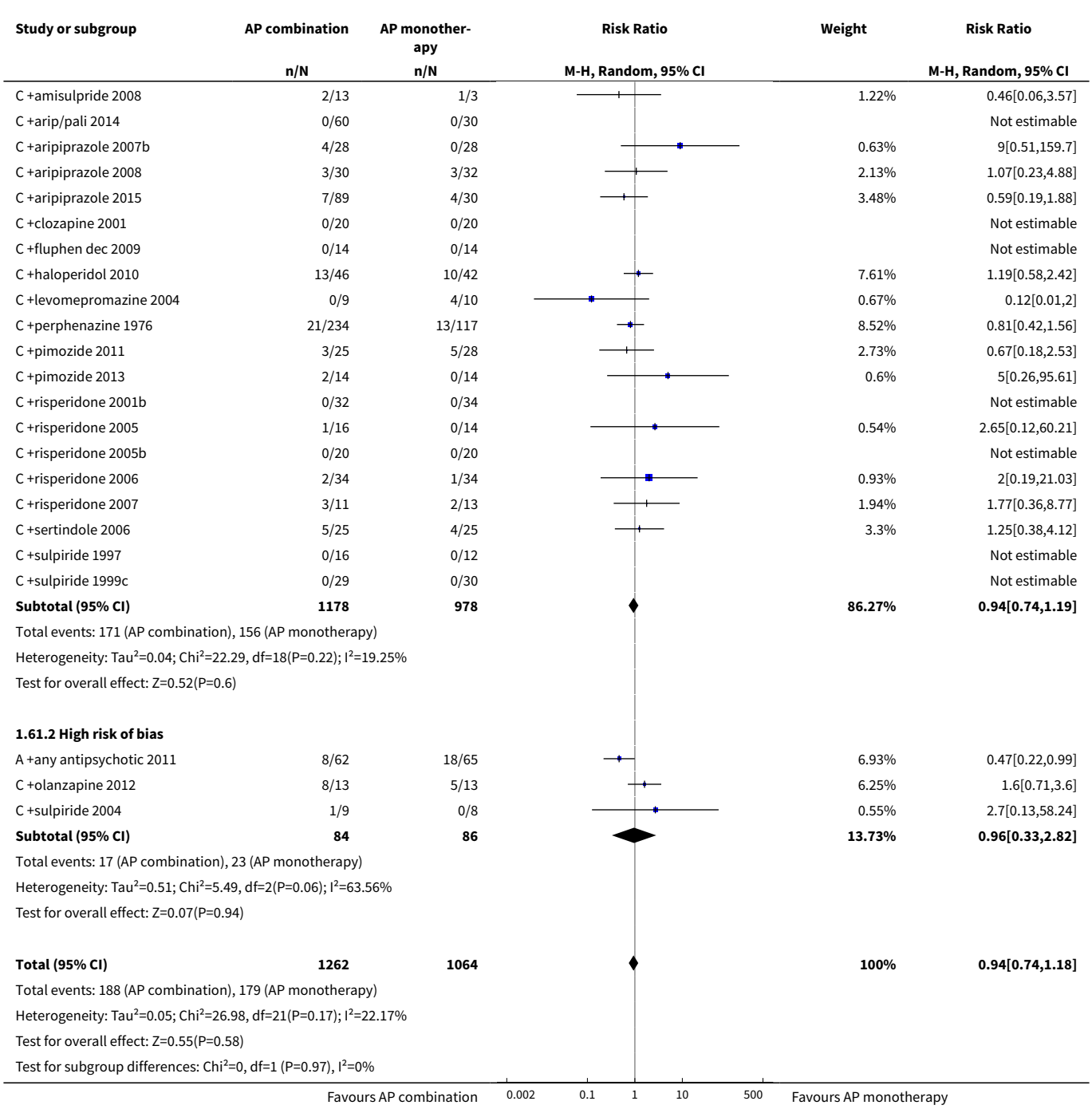
Study or subgroup	AP combination n/N	AP monotherapy n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.60.1 Low / unclear risk of bias					
A +any antipsychotic 2011	8/62	18/65		6.93%	0.47[0.22,0.99]
A +pimozide 1985	27/47	42/46		20.11%	0.63[0.48,0.82]
A +reserpine 1957	0/10	2/22		0.6%	0.42[0.02,7.99]
A +trifluoperazine 1964	0/27	0/50			Not estimable
B +aripiprazole 2008	11/108	6/99		4.8%	1.68[0.65,4.37]
B +aripiprazole 2011	6/20	3/20		3.08%	2[0.58,6.91]
B +quet/risp 2009	53/168	48/155		17.69%	1.02[0.74,1.41]
B +risperidone 2010	8/33	8/36		5.71%	1.09[0.46,2.57]
C +amisulpride 2008	2/13	1/3		1.22%	0.46[0.06,3.57]
C +arip/pali 2014	0/60	0/30			Not estimable
C +aripiprazole 2007b	4/28	0/28		0.63%	9[0.51,159.7]
C +aripiprazole 2008	3/30	3/32		2.13%	1.07[0.23,4.88]
C +aripiprazole 2015	7/89	4/30		3.48%	0.59[0.19,1.88]





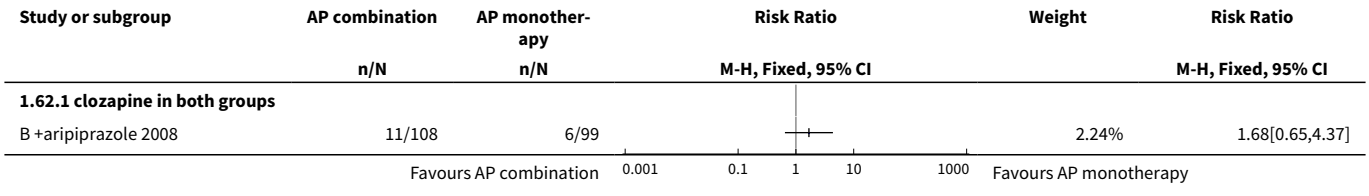
Analysis 1.61. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 61 SENSITIVITY ANALYSIS Leaving the study early - Double blind.



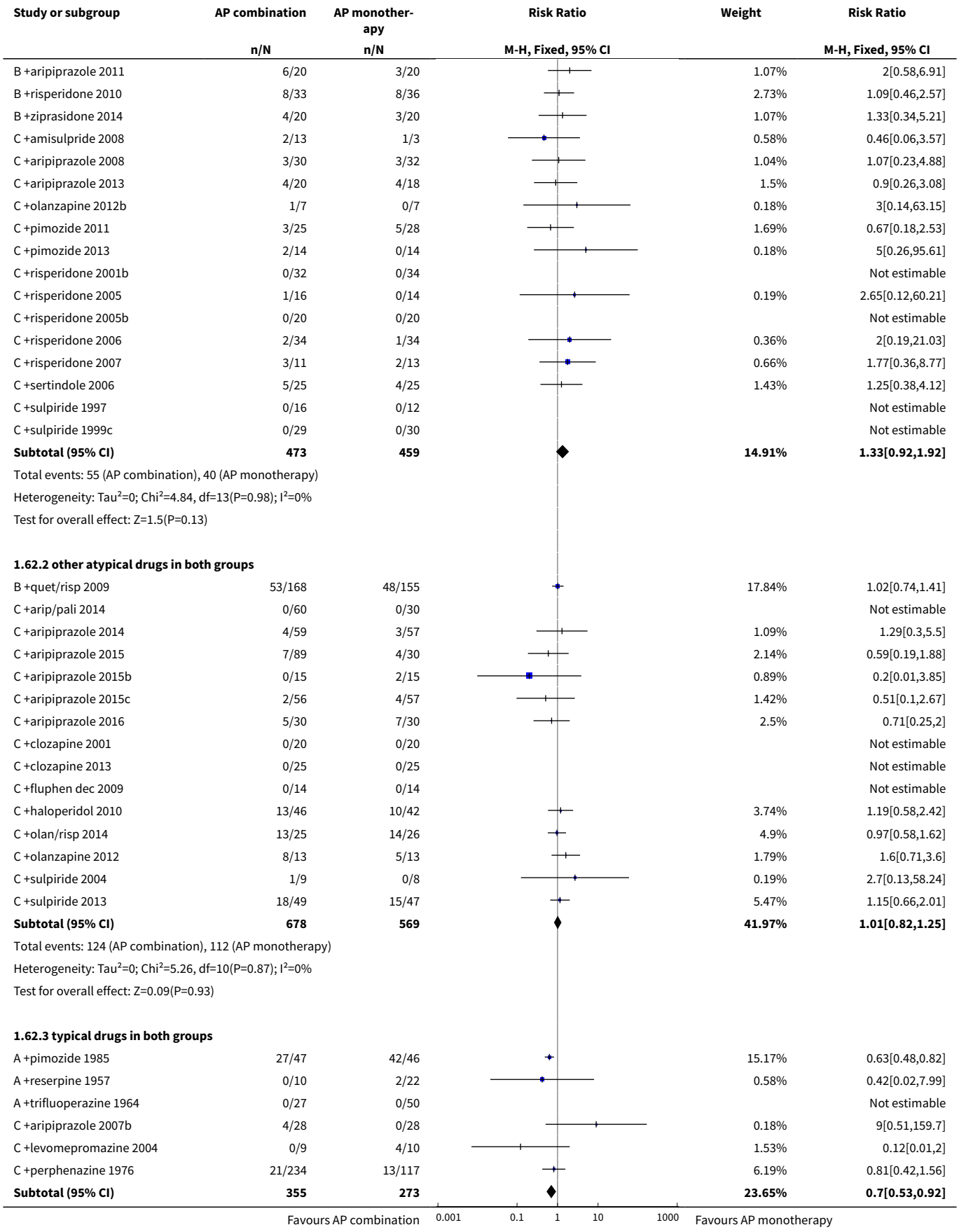


Study or subgroup	AP combination n/N	AP monotherapy n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
C +amisulpride 2008	2/13	1/3		1.22%	0.46[0.06,3.57]
C +arip/pali 2014	0/60	0/30			Not estimable
C +aripiprazole 2007b	4/28	0/28		0.63%	9[0.51,159.7]
C +aripiprazole 2008	3/30	3/32		2.13%	1.07[0.23,4.88]
C +aripiprazole 2015	7/89	4/30		3.48%	0.59[0.19,1.88]
C +clozapine 2001	0/20	0/20			Not estimable
C +fluphen dec 2009	0/14	0/14			Not estimable
C +haloperidol 2010	13/46	10/42		7.61%	1.19[0.58,2.42]
C +levomepromazine 2004	0/9	4/10		0.67%	0.12[0.01,2]
C +perphenazine 1976	21/234	13/117		8.52%	0.81[0.42,1.56]
C +pimozide 2011	3/25	5/28		2.73%	0.67[0.18,2.53]
C +pimozide 2013	2/14	0/14		0.6%	5[0.26,95.61]
C +risperidone 2001b	0/32	0/34			Not estimable
C +risperidone 2005	1/16	0/14		0.54%	2.65[0.12,60.21]
C +risperidone 2005b	0/20	0/20			Not estimable
C +risperidone 2006	2/34	1/34		0.93%	2[0.19,21.03]
C +risperidone 2007	3/11	2/13		1.94%	1.77[0.36,8.77]
C +sertindole 2006	5/25	4/25		3.3%	1.25[0.38,4.12]
C +sulpiride 1997	0/16	0/12			Not estimable
C +sulpiride 1999c	0/29	0/30			Not estimable
Subtotal (95% CI)	**1178**	**978**		**86.27%**	**0.94[0.74,1.19]**
Total events: 171 (AP combination), 156 (AP monotherapy)					
Heterogeneity: Tau²=0.04; Chi²=22.29, df=18(P=0.22); I²=19.25%					
Test for overall effect: Z=0.52(P=0.6)					
1.61.2 High risk of bias					
A +any antipsychotic 2011	8/62	18/65		6.93%	0.47[0.22,0.99]
C +olanzapine 2012	8/13	5/13		6.25%	1.6[0.71,3.6]
C +sulpiride 2004	1/9	0/8		0.55%	2.7[0.13,58.24]
Subtotal (95% CI)	**84**	**86**		**13.73%**	**0.96[0.33,2.82]**
Total events: 17 (AP combination), 23 (AP monotherapy)					
Heterogeneity: Tau²=0.51; Chi²=5.49, df=2(P=0.06); I²=63.56%					
Test for overall effect: Z=0.07(P=0.94)					
Total (95% CI)	**1262**	**1064**		**100%**	**0.94[0.74,1.18]**
Total events: 188 (AP combination), 179 (AP monotherapy)					
Heterogeneity: Tau²=0.05; Chi²=26.98, df=21(P=0.17); I²=22.17%					
Test for overall effect: Z=0.55(P=0.58)					
Test for subgroup differences: Chi²=0, df=1 (P=0.97), I²=0%					

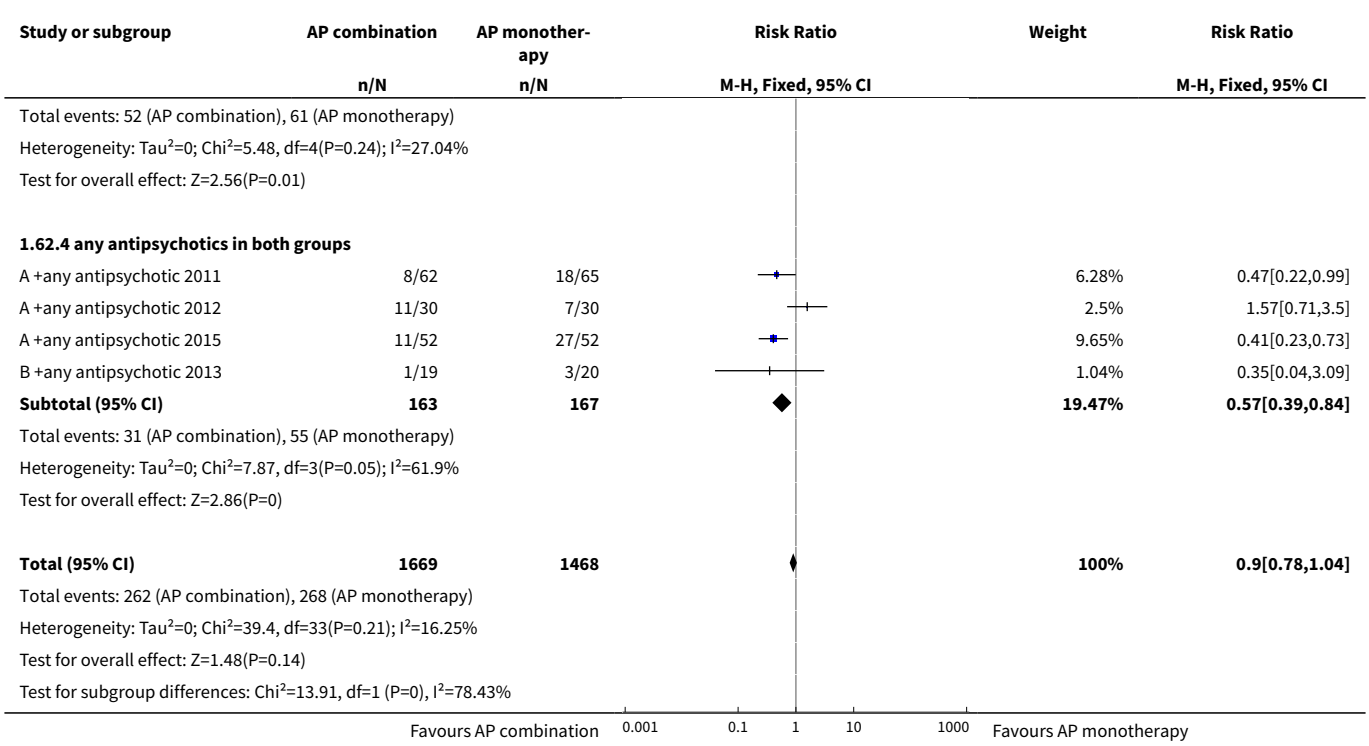
Analysis 1.62. Comparison 1 ANTIPSYCHOTIC COMBINATIONS vs ANTIPSYCHOTIC MONOTHERAPY, Outcome 62 SENSITIVITY ANALYSIS Leving the study early - Fixed effect.



Study or subgroup	AP combination n/N	AP monotherapy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.62.1 clozapine in both groups					
B +aripiprazole 2008	11/108	6/99		2.24%	1.68[0.65,4.37]



Study or subgroup	AP combination	AP monotherapy	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
B +aripiprazole 2011	6/20	3/20		1.07%	2[0.58,6.91]
B +risperidone 2010	8/33	8/36		2.73%	1.09[0.46,2.57]
B +ziprasidone 2014	4/20	3/20		1.07%	1.33[0.34,5.21]
C +amisulpride 2008	2/13	1/3		0.58%	0.46[0.06,3.57]
C +aripiprazole 2008	3/30	3/32		1.04%	1.07[0.23,4.88]
C +aripiprazole 2013	4/20	4/18		1.5%	0.9[0.26,3.08]
C +olanzapine 2012b	1/7	0/7		0.18%	3[0.14,63.15]
C +pimozide 2011	3/25	5/28		1.69%	0.67[0.18,2.53]
C +pimozide 2013	2/14	0/14		0.18%	5[0.26,95.61]
C +risperidone 2001b	0/32	0/34			Not estimable
C +risperidone 2005	1/16	0/14		0.19%	2.65[0.12,60.21]
C +risperidone 2005b	0/20	0/20			Not estimable
C +risperidone 2006	2/34	1/34		0.36%	2[0.19,21.03]
C +risperidone 2007	3/11	2/13		0.66%	1.77[0.36,8.77]
C +sertindole 2006	5/25	4/25		1.43%	1.25[0.38,4.12]
C +sulpiride 1997	0/16	0/12			Not estimable
C +sulpiride 1999c	0/29	0/30			Not estimable
Subtotal (95% CI)	**473**	**459**		**14.91%**	**1.33[0.92,1.92]**
Total events: 55 (AP combination), 40 (AP monotherapy)					
Heterogeneity: Tau^2=0; Chi^2=4.84, df=13(P=0.98); I^2=0%					
Test for overall effect: Z=1.5(P=0.13)					
1.62.2 other atypical drugs in both groups					
B +quet/risp 2009	53/168	48/155		17.84%	1.02[0.74,1.41]
C +arip/pali 2014	0/60	0/30			Not estimable
C +aripiprazole 2014	4/59	3/57		1.09%	1.29[0.3,5.5]
C +aripiprazole 2015	7/89	4/30		2.14%	0.59[0.19,1.88]
C +aripiprazole 2015b	0/15	2/15		0.89%	0.2[0.01,3.85]
C +aripiprazole 2015c	2/56	4/57		1.42%	0.51[0.1,2.67]
C +aripiprazole 2016	5/30	7/30		2.5%	0.71[0.25,2]
C +clozapine 2001	0/20	0/20			Not estimable
C +clozapine 2013	0/25	0/25			Not estimable
C +fluphen dec 2009	0/14	0/14			Not estimable
C +haloperidol 2010	13/46	10/42		3.74%	1.19[0.58,2.42]
C +olan/risp 2014	13/25	14/26		4.9%	0.97[0.58,1.62]
C +olanzapine 2012	8/13	5/13		1.79%	1.6[0.71,3.6]
C +sulpiride 2004	1/9	0/8		0.19%	2.7[0.13,58.24]
C +sulpiride 2013	18/49	15/47		5.47%	1.15[0.66,2.01]
Subtotal (95% CI)	**678**	**569**		**41.97%**	**1.01[0.82,1.25]**
Total events: 124 (AP combination), 112 (AP monotherapy)					
Heterogeneity: Tau^2=0; Chi^2=5.26, df=10(P=0.87); I^2=0%					
Test for overall effect: Z=0.09(P=0.93)					
1.62.3 typical drugs in both groups					
A +pimozide 1985	27/47	42/46		15.17%	0.63[0.48,0.82]
A +reserpine 1957	0/10	2/22		0.58%	0.42[0.02,7.99]
A +trifluoperazine 1964	0/27	0/50			Not estimable
C +aripiprazole 2007b	4/28	0/28		0.18%	9[0.51,159.7]
C +levomepromazine 2004	0/9	4/10		1.53%	0.12[0.01,2]
C +perphenazine 1976	21/234	13/117		6.19%	0.81[0.42,1.56]
Subtotal (95% CI)	**355**	**273**		**23.65%**	**0.7[0.53,0.92]**



ADDITIONAL TABLES

Table 1. Meta-regression

	Estimate	SE	95% CI		P value
			Lower	Upper	
Intercept	-29.5401	26.5608	-81.5983	22.5181	0.2661
Year	0.0147	0.0133	-0.0114	0.0408	0.2706
Chinese	64.7592	120.7041	-171.8166	301.3349	0.5916
Year*Chinese (interaction)	-0.0326	0.0603	-0.1508	0.0857	0.5895

tau² (estimated amount of residual heterogeneity): 0.8884 (SE = 0.4106)
tau (square root of estimated tau² value): 0.9426
I² (residual heterogeneity / unaccounted variability): 97.91%
H² (unaccounted variability / sampling variability): 47.80%
R² (amount of heterogeneity accounted for): 0.00%

Table 2. Suggested design of future study

Methods	**Allocation**: randomised - clearly described generation of sequence and concealment of allocation. **Blindness**: double - described and tested. **Duration**: 12 months minimum.

Table 2. Suggested design of future study *(Continued)*

Participants	**Diagnosis:** schizophrenia (operational criteria). **N** = 600. * **Age:** any. **Gender:** both. **History:** any.
Interventions	1. Antipsychotic combination. N = 300. 2. Antipsychotic of choice. N = 300.
Outcomes	• Global impression: CGI**, relapse, clinical improvement. • Leaving study early (any reason, adverse events, inefficacy). • Service outcomes: hospitalised, time in hospital, attending out patient clinics. • Adverse events: major and minor problems as perceived by participant and clinician. • Employment, family satisfaction, patient satisfaction. • Quality of life: simple binary rating.

* power calculation suggested 300/group would allow good chance of showing a 10% difference between groups for primary outcome.
** Primary outcome.
CGI - Clinical Global Impression.

APPENDICES

Appendix 1. Checklist to aid consistency and reproducibility of GRADE assessments

Trial limitations		SoF outcome 1 (Clinical response: No clinical improvement)	SoF outcome 3(Leaving the study early)	SoF outcome 4 (Service utilization: Hospital admission)	SoF outcome 6 (Adverse events: Serious event or requiring discontinuation)
Risk of bias[a]	Was random sequence generation used (i.e. no potential for selection bias)?	**Unclear**	**Yes**	**Unclear**	**Unclear**
	Was allocation concealment used (i.e. no potential for selection bias)?	**Unclear**	**Unclear**	**Yes**	**Yes**
	Was there blinding of participants and personnel (i.e. no potential for performance bias) or outcome not likely to be influenced by lack of blinding?	**Unclear**	**Unclear**	**Unclear**	**Unclear**
	Was there blinding of outcome assessment (i.e. no potential for detection bias) or was outcome measurement not likely to be influenced by lack of blinding?	**Unclear**	**Unclear**	**Unclear**	**No (*)**
	Was an objective outcome used?	**No (*)**	**Yes**	**Yes**	**Yes**
	Were more than 80% of participants enrolled in trials included in the analysis (i.e. no potential reporting bias)?[e]	**Unclear**	**Yes**	**Unclear**	**Unclear**

(Continued)

	Were data reported consistently for the outcome of interest (i.e. no potential selective reporting)?	**Unclear**	**Yes**	**Unclear**	**Yes**
	No other biases reported (i.e. no potential of other bias)?	**Yes**	**Yes**	**Yes**	**Yes**
	Did the trials end up as scheduled (i.e. not stopped early)?	**Yes**	**Yes**	**Yes**	**Yes**
Inconsistency[b]	Point estimates did not vary widely?	**Yes**	**No(*)**	**Yes**	**No(*)**
	To what extent did confidence intervals overlap (substantial: all confidence intervals overlap at least one of the included studies point estimate; some: confidence intervals overlap but not all overlap at least one point estimate; no: at least one outlier: where the confidence interval of some of the studies do not overlap with those of most included studies)?	**Some**	**Some**	**Some**	**Some**
	Was the direction of effect consistent?	**Yes**	**No (*)**	**No (*)**	**No (*)**
	What was the magnitude of statistical heterogeneity (as measured by I^2) - low (I^2 < 40%), moderate (I^2 40%-60%), high I^2 > 60%)?	**High (*)**	**Low**	**Low**	**Low**
	Was the test for heterogeneity statistically significant (P < 0.1)?	**Statistically significant (*)**	**Not statistically significant**	**Not statistically significant**	**Not statistically significant**
Indirectness	Were the populations in included studies applicable to the decision context?	**Applicable**	**Applicable**	**Applicable**	**Applicable**
	Were the interventions in the included studies applicable to the decision context?	**Highly applicable**	**Applicable**	**Applicable**	**Applicable**
	Was the included outcome not a surrogate outcome?	**Yes**	**Yes**	**Yes**	**Yes**
	Was the outcome timeframe sufficient?	**Insufficient (*)**	**Sufficient**	**Insufficient (*)**	**Insufficient (*)**
	Were the conclusions based on direct comparisons?	**Yes**	**Yes**	**Yes**	**Yes**
Imprecision[c]	Was the confidence interval for the pooled estimate not consistent with benefit and harm?	**Yes**	**No (*)**	**No (*)**	**No (*)**
	What is the magnitude of the median sample size (high: 300 participants, intermedi-	**High**	**High**	**Intermediate**	**High**

(Continued)

	ate: 100-300 participants, low: <100 participants)?[e]				
	What was the magnitude of the number of included studies (large: > 10 studies, moderate: 5-10 studies, small: < 5 studies)?[e]	**Large**	**Large**	**Small (*)**	**Large**
	Was the outcome a common event (e.g. occurs more than 1/100)?	**Yes**	**Yes**	**Yes**	**Yes**
Publication bias[d]	Was a comprehensive search conducted?	**Yes**	**Yes**	**Yes**	**Yes**
	Was grey literature searched?	**Yes**	**Yes**	**Yes**	**Yes**
	Were no restrictions applied to study selection on the basis of language?	**Yes**	**Yes**	**Yes**	**Yes**
	There was no industry influence on studies included in the review?	**Yes**	**Yes**	**Yes**	**No (*)**
	There was no evidence of funnel plot asymmetry?	**No (*)**	**Yes**	**N/A**	**Yes**
	There was no discrepancy in findings between published and unpublished trials?	**Unclear**	**Unclear**	**Unclear**	**Unclear**

Footnotes

[a]Questions on risk of bias are answered in relation to the majority of the aggregated evidence in the meta-analysis rather than to individual trials

[b]Questions on inconsistency are primarily based on visual assessment of forest plots and the statistical quantification of heterogeneity based on I^2 statistic

[c]When judging the width of the confidence interval it is recommended to use a clinical decision threshold to assess whether the imprecision is clinically meaningful

[d]Questions address comprehensiveness of the search strategy, industry influence, funnel plot asymmetry and discrepancies between published and unpublished trials

[e]Depends on the context of the systematic review area

(*): key item for potential downgrading the quality of the evidence (GRADE) as shown in the footnotes of the 'Summary of findings' table; GRADE: Grading of Recommendations Assessment, Development and Evaluation; N/A: not applicable

Appendix 2. Initial trial selection and data extraction

Two review authors (NM, KSW) inspected all abstracts of studies identified as above and identified potentially relevant reports. JX screened the Chinese language studies. Where disagreement occurred this was resolved by discussion, or where there was still doubt, the full article was acquired for further inspection. We acquired the full articles of relevant reports for reassessment and carefully inspected for a final decision on inclusion (see Criteria for considering studies for this review). NM and KSW were not blinded to the names of the authors, institutions or journal of publication. Where difficulties or disputes arose, we asked author CEA for help and where it was impossible to decide or if adequate information was not available to make a decision, we added these studies to those awaiting assessment and the authors of the papers contacted for clarification.

1. Extraction

Review authors NM and KSW extracted data from all included studies. In addition, JX extracted data for all Chinese studies and one study in Japanese was inspected by IO. To ensure reliability, CEA independently extracted data from a random sample of these studies, comprising 30% of the total. Again, any disagreement was discussed, decisions documented and, if necessary, authors of studies contacted for

clarification. With remaining problems CEA helped clarify issues and those final decisions were documented. We extracted data presented only in graphs and figures whenever possible, but only included if two review authors independently had the same result. Where possible, we extracted data relevant to each component centre of multi-centre studies separately.

2. Management

2.1 Forms

A form for data collection was created in Microsoft InfoPath 2007, piloted in three trials independently by two authors, and revised after author discussion. We extracted data onto these forms.

Assessment of risk of bias in included studies

KSW and NM independently assessed the risk of bias of each trial published in English and JX assessed trials published in Chinese using Cochrane's 'Risk of bias' tool (Higgins 2011). This set of criteria is based on evidence of associations between overestimate of effect and high risk of bias of the article such as sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting. If the raters disagreed, the final rating was made by consensus, with the involvement of another member of the review group. Where inadequate details of randomisation and other characteristics of trials were provided, authors of the studies were contacted in order to obtain further information. Non-concurrence in quality assessment was reported, but if disputes arise as to which category a trial is to be allocated, again, resolution was made by discussion with CEA. The level of risk of bias was noted in both the text of the review and in the 'Summary of findings' table 1.

Data synthesis

We understand that there is no closed argument for preference for use of fixed-effect or random-effects models. The random-effects method incorporates an assumption that the different studies are estimating different, yet related, intervention effects. This often seems to be true to us and the random-effects model takes into account differences between studies even if there is no statistically significant heterogeneity. There is, however, a disadvantage to the random-effects model. It puts added weight onto small studies which often are the most biased ones. Depending on the direction of effect these studies can either inflate or deflate the effect size. A fixed-effect model was used, unless we demonstrated statistically significant heterogeneity ($P < 0.10$) for a specific outcome, in which case the random-effects models was preferred.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses - only primary outcomes

For subgroup and sensitivity analyses the random-effects model was used for all analyses for which an I^2 was above 50%. Subgroup and sensitivity analyses were undertaken only where there were at least 10 trials. In addition, trials with zero events were not accounted for in the subgroup analyses.

1.1 Leaving the study early

We undertook four subgroup analyses using data from the primary outcome 'leaving the study early':

- enrolment of acutely exacerbated or chronically ill patients;
- treatment duration < 12 weeks versus ≥ 12 weeks;
- clozapine versus non-clozapine combinations; and
- drug added to co-treatment of the same antipsychotics in combination or monotherapy groups.

Appendix 3. Participant's country of origin

Country of origin	Number of trials	Number of participants
China	24	2222
Europe	6	367
Iran	1	28
Israel	2	45
Japan	7	594

(Continued)

Korea	2	96
Multinational	1	68
Taiwan	2	184
Turkey	1	30
USA	12	975
Unclear	2	70

Appendix 4. Operational criteria

Operational criteria		Number of trials
Diagnostic and Statistical Manual of Mental Disorders	DSM-IV	31
	DSM-III	2
	DSM-II	1
International Classification of Diseases	ICD-10	2
Chinese Classification of Mental Disorders	CCMD-III	5
	CCMD-2R	8
Unclear		13

Appendix 5. Antipsychotic doses

Clozapine in both groups

Study ID	MONOTHERAPY				COMBINATION			
	Arm 1		Arm 2		Arm 1		Arm 2	
	Drug	Dose	Drug	Dose	Drug	Dose	Drug	Dose
A +sulpiride 1994	Clozapine	265 SD 101 mg/d	Sulpride	1077 SD 196 mg/d	Clozapine	84 SD 48 mg/d	-	-
					Sulpiride	mean 911 SD 97 mg/d	-	-
B +aripiprazole 2008	Clozapine	163 mg to 900 mg/d	-	-	Clozapine	163 mg to 900 mg/ d	-	-
					Aripiprazole	5 mg to 15 mg/d	-	-
B +aripiprazole 2011	Clozapine	200 mg to 450 mg/d	-	-	Clozapine	(200 mg to 450 mg/d	-	-
					Aripiprazole	10 mg to 15 mg/d	-	-
B +pipotiazine 2002	Clozapine	200 mg˜450 mg/d	-	-	Clozapine	200 mg˜450 mg/d	-	-
					Pipotiazine	50 mg once, followed by 50 mg˜100mg once every 4 weeks	-	-
B +risperidone 2010	Clozapine	Not reported	-	-	Clozapine	Not reported	-	-
					Risperidone	4 mg/d	-	-
B +sulpiride 1996	Clozapine	486.77 mg ± 29.81 mg/d	Sulpride	1296.86 mg ± 105.11mg	Clozapine	436.57 mg ± 89.85 mg/d	-	-
					Sulpiride	1127.23 mg ± 156.55 mg/d	-	-
B +ziprasidone 2014	Clozapine	350 mg to 600 mg/d	-	-	Clozapine	350 mg to 600 mg/d	-	-
					Ziprasidone	80 mg/day	-	-
C +amisulpride 2008	Clozapine	300 mg/d	-	-	Clozapine	300 mg/d	Clozapine	300 mg/d
					Amisulpiride	400 mg/d	Amisulpiride	600 mg/d
C +aripiprazole 2008	Clozapine	400 mg/d	-	-	Clozapine	400 mg/d	-	-

(Continued)

					Aripiprazole	5 mg to 30 mg/d	-	-
C +aripiprazole 2013	Clozapine	Mean 400 mg (139 SD)	-	-	Clozapine	Mean 397 mg (144 SD)	-	-
					Aripiprazole	15 mg/d	-	-
C +CPZ 1989	Clozapine	50 mg to 600 mg	Chlorpromazine	100 mg to 600mg	Clozapine	max 400 mg	-	-
					Chlorpromazine	max 400 mg	-	-
C +CPZ 1999	Clozapine	300 mg/d	Chlorpromazine	400 mg/d	Clozapine	300 mg/d	-	-
					Chlorpromazine	100 mg/d	-	-
C +haloperidol 2006	Clozapine	mean 500 mg/d (SD 81.6)	-	-	Clozapine	Mean 450 mg/d (SD 70.7)	-	-
					Haloperidol	4 mg/d	-	-
C +olanzapine 2012b	Clozapine	Not reported	-	-	Clozapine	Not reported	-	-
					Olanzapine	Not reported	-	-
C +pimozide 2011	Clozapine	mean 478.1 mg/d (150.2 SD)	-	-	Clozapine	Mean 518.8 mg (117.3 SD)	-	-
					Pimozide	mean 6.48 mg/d (2.18 SD) max 8 mg/d	-	-
C +pimozide 2013	Clozapine	Mean 519 ng/mL	-	-	Clozapine	Mean 650 ng/mL	-	-
					Pimozide	Max dose 4 mg	-	-
C +pipotiazine 2000	Clozapine	489.81 mg ± 29.73 mg/d	-	-	Clozapine	491.62 mg ± 30.68 mg/d	-	-
					Pipotiazine	25 mg administered through muscle injection at the start of the trial, a further 50 mg was administered two weeks later. After that, 50 mg~100 mg/month until the end of trial)	-	-
C +risperidone 2001	Clozapine	375 mg ± 112 mg/d	Risperidone	4.3 mg ± 1.2mg/d	Clozapine	150 mg ± 72 mg/d	-	-

(Continued)

					Risperidone	1.5 mg ± 1.3 mg/d	-	-
C +risperidone 2001b	Clozapine	≤ 600 mg	Risperidone	≤8 mg	Clozapine	200 mg	-	-
					Risperidone	6 mg	-	-
C +risperidone 2001c	Clozapine	50 mg to 400 mg/d	Risperidone	1 mg to 6 mg/d	Clozapine	average˜100 mg/d	-	-
					Risperidone	1 mg to 4 mg/d	-	-
C +risperidone 2005	Clozapine	600 mg to 900 mg/d	-	-	Clozapine	600 mg to 900 mg/d	-	-
					Risperidone	2 mg to 6 mg/d	-	-
C +risperidone 2005b	Clozapine	Not reported	-	-	Clozapine	Not reported	-	-
					Risperidone	1 mg to 6 mg/d	-	-
C +risperidone 2006	Clozapine	490 mg/d	-	-	Clozapine	490 mg/d	-	-
					Risperidone	1 mg to 3 mg/d	-	-
C +risperidone 2007	Clozapine	456 mg/d average (200 mg to 700 mg/d)	-	-	Clozapine	456 mg/d average (200 mg to 700 mg/d)	-	-
					Risperidone	4 mg/d	-	-
C +sertindole 2006	Clozapine	mean 435.0 (197.8 SD)	-	-	Clozapine	Mean 394.0 (148.1 SD)	-	-
					Sertindole	16 mg/d	-	-
C +sulpiride 1997	Clozapine	400 mg to 450 mg/d	-	-	Clozapine	400 mg to 450 mg/d	-	-
					Sulpiride	600 mg/d	-	-
C +sulpiride 1999	Clozapine	486.17 mg ± 30.8mg/d	Sulpride	1390.2 mg ± 104.86mg/d	Clozapine	25 mg˜75 mg/d	-	-
					Sulpiride	1390.2 mg ± 104.86 mg/d	-	-
C +sulpiride 1999b	Clozapine	350 mg/d	-	-	Clozapine	350 mg/d	-	-

(Continued)

					Sulpride	800 mg/d	-	-
C +sulpiride 1999c	Clozapine	50 mg to500 mg/d	-	-	Clozapine	50 mg to 500 mg/d	Clozapine	50 mg to 500 mg/d
					Sulpiride	0.2 mg to 1 mg/d	Chlorim-ipramine	50 mg to 150 mg/d
C +sulpiride 2003	Clozapine	150 mg˜300 mg/d	Sulpride	300 mg˜600 mg/d	Clozapine	150 mg˜300 mg/d	-	-
					Sulpride	300 mg˜600 mg/d	-	-
C +sulpiride 2006	Clozapine	25 mg twice daily	-	-	Clozapine	25 mg twice daily	-	-
					Sulpride	200 mg˜600 mg/d	-	-

Footnotes
d - day

Other atypical drugs in both groups

Study ID	MONOTHERAPY				COMBINATION					
	Arm 1		Arm 2		Arm 1		Arm 2		Arm 3	
	Drug	Dose	Drug	Dose	Drug	Dose	Drug	Dose	Drug	Dose
B +quet/risp 2009	Quetiapine	400 mg to 800 mg/d	Risperidone	4 mg to 8 mg/d	Quetiapine	400 mg to 800 mg/d	Risperidone	4 mg to 8 mg/d	-	-
					Aripiprazole	2 mg to 15 mg/d	Aripiprazole	2 mg to 15 mg/d	-	-
C +aripiprazole 2007	Sulpiride	500 mg to 900 mg	-	-	Sulpiride	600 mg to 900 mg	-	-	-	-
					Aripiprazole	10 mg	-	-	-	-
C +aripiprazole 2012	Risperidone	2 mg to 12 mg/d	Olanzapine	2.5 mg to 20 mg/d	Risperidone	2 mg to 12 mg/d	Olanzapine	2.5 mg to 20 mg/d	-	-
					Aripiprazole	6 mg to 30 mg/d	Aripiprazole	6 mg to 30 mg/d	-	-
C +aripiprazole 2013b	Risperidone	3 mg to 6 mg	-	-	Risperidone	3 mg to 6 mg	-	-	-	-
					Aripiprazole	10 mg/day	-	-	-	-
C +aripiprazole 2014	Risperidone	3 mg to 8 mg/day	-	-	Risperidone	3 mg to 8 mg/day	-	-	-	-
					Aripiprazole	10 mg to 20 mg/day	-	-	-	-
C +aripiprazole 2015	Risperidone	mean = 4.93 mg/day SD 1.05	-	-	Risperidone	mean = 4.63 mg/day SD 1.10	Risperidone	mean = 4.79 mg/day SD 1.01	Risperidone	mean = 5.07 mg/day SD 1.12
					Aripiprazole	5 mg/d	Aripiprazole	10 mg/d	Aripiprazole	20 mg/d
C +aripiprazole 2015b	Risperidone	mean 6 mg/day	-	-	Risperidone	mean 6 mg/day	-	-	-	-
					Aripiprazole	10 mg/day	-	-	-	-

(Continued)

C +aripiprazole 2015c	Risperidone	4 mg to 6 mg/day	-	-	Risperidone	4 mg to 6 mg/day	-	-	-	-
					Aripiprazole	10 mg/day	-	-	-	-
C +aripiprazole 2016	Paliperidone	6 mg to 12 mg/day	Risperidone	3 mg to 6 mg/day	Paliperidone	6 mg to 12 mg/day	Risperidone	3 mg to 6 mg/day	-	-
					Aripiprazole	5 mg/day	Aripiprazole	5 mg/day	-	-
C +arip/pali 2014	Olanzapine	10 mg	-	-	Olanzapine	10 mg	Olanzapine	10 mg/d	-	-
					Aripiprazole	10 mg/d	Paliperidone	3 mg/d	-	-
C +clozapine 2001	Risperidone	4 mg to 6 mg/d	-	-	Clozapine	50 mg to 300 mg/d	-	-	-	-
					Risperidone	4 mg to 6 mg/d	-	-	-	-
C +clozapine 2013	Atypical antipsychotic	No dose reported	-	-	Atypical antipsychotic	No dose reported	-	-	-	-
					Clozapine	300 mg to 400 mg/day	-	-	-	-
C +fluphendec 2009	Olanzapine	15 mg to 25 mg/d	-	-	Olanzapine	15 mg to 25 mg/d	-	-	-	-
					Fluphenazine Decanoate	Week zero 6.25 mg/2 weeks IM, and increased by 6.25 mg increments, as needed or tolerated, in biweekly intervals, to a maximum of 25 mg/2 weeks by week eight.	-	-	-	-
C +haloperidol 2010	Risperidone	4 mg/d	-	-	Risperidone	2 mg/d	-	-	-	-
					Haloperidol	2 mg/d	-	-	-	-

(Continued)

C +olanzapine 2012	Risperidone	Starting at 3 mg/d, at 2 weeks < 6 mg/d was allowed and at 8 weeks <12 mg/d	-	-	Risperidone	< 6 mg/d	-	-	-	-
					Olanzapine	< 20 mg/d	-	-	-	-
C +olan/risp 2014	Olanzapine	Max 18.8 mg/day	Risperidone	Max 8.2 mg/day	Olanzapine	Mean 19.0 mg/day	Risperidone	Mean 8.7 mg/day	-	-
					Risperidone	Max 8.1 mg/day	Olanzapine	Max. 16.1 mg/day	-	-
C +sulpiride 2004	Olanzapine	20 mg to 30 mg/d	-	-	Olanzapine	20 mg to 30 mg/d	-	-	-	-
					Sulpiride	100 mg to 600 mg/d	-	-	-	-
C +sulpiride 2013	Amisulpride	800mg/day	-	-	Amisulpride	400 mg/day	-	-	-	-
					Sulpiride	800 mg/day	-	-	-	-

Footnotes

d - day

Typical in both groups

Study ID	MONOTHERAPY				COMBINATION			
	Arm 1		Arm 2		Arm 1		Arm 2	
	Drug	Dose	Drug	Dose	Drug	Dose	Drug	Dose
A +pimozide 1985	Thioridazine	25 mg or 75 mg	Pimozide	2 mg or 6 mg	Thioridazine	25 mg or 75 mg	-	-
					Pimozide	2 mg or 6 mg	-	-
A +reserpine 1957	Chlorpro-mazine	200 mg to1200 mg/d	Reserpine	4 mg to 8 mg/d	Chlorpromazine	100 mg to 400mg/d	-	-
					Reserpine	1 mg to 4 mg/d	-	-
A +trifluoperazine 1964	Chlorpro-mazine	150 mg to 300 mg	Trifluoper-azine	5 mg to 10 mg	Chlorpromazine	150 mg to 300 mg	-	-
					Trifluoperazine	5 mg to 10 mg	-	-
C +aripiprazole 2007b	Haloperidol	Not reported	-	-	Haloperidol	Not reported	-	-
					Aripiprazole	15 mg to 30 mg/d	-	-
C +aripiprazole 2008b	Chlorpro-mazine	200 mg˜450 mg/d	-	-	Chlorpromazine	200 mg˜450 mg/d	-	-
					Aripiprazole	5 mg/d	-	-
C +aripiprazole 2009	Haloperidol	Not reported	-	-	Haloperidol	Not reported	-	-
					Aripiprazole	5 mg/d	-	-
C +CPZ 1973	Chlorpro-mazine	388 mg/d	Fluphenazine enanthate	28.5 mg every 11.5 days	Chlorpromazine	349.6 mg/d	-	-
					Fluphenazine enan-thate	26 mg every 11.5 days	-	-
C +levomepro-mazine 2004	Haloperidol	Not reported	-	-	Haloperidol	Not reported	-	-
					Levomepromazine	Not reported, except dose ratio was fixed at 1:10	-	-

(Continued)

C +perphenazine 1976	Chlorpro-mazine	75 mg to 200 mg/d	-	-	Chlorpromazine	75 mg to 200 mg/d	Chlorpro-mazine	75 mg to 200 mg/d
					Carpipramine	Not reported	Per-phenazine	Not report-ed

Footnotes

d - day

Any antipsychotic in both groups

Study ID	MONOTHERAPY		COMBINATION	
	Arm 1		Arm 1	
	Drug	Dose	Drug	Dose
A +any antipsychotic 2011	Switch to antipsychotic monotherapy	Mean haloperidol equivalent = 7.2 mg/day Mean chlorpromazine equivalent = 387.8 mg/d	Most common antipsychotic combinations were quetiapine and risperidone, quetiapine and a first-generation antipsychotic, risperidone and a first-generation antipsychotic, olanzapine and a first-generation antipsychotic, ziprasidone and a first-generation antipsychotic, aripiprazole and quetiapine and olanzapine and risperidone.	Mean haloperidol equivalent 6.1 mg/day Mean chlorpromazine equivalent 325.8 mg/d
A +any antipsychotic 2012	Switch to dual antipsychotics by adding up another medication, choice of medication to add was left to prescriber and patient a the dose of all drug could be raised or lowered	No dose reported	Previous monotherapy Choice of medication to add was left to prescriber and patient	Dose of all drugs could be raised or lowered at the discretion of the prescriber
B +any antipsychotic 2013	Switch to antipsychotic monotherapy	Mean chlorpromazine equivalent = 552.9 mg/d	Most common baseline polypharmacy combination were: risperidone and a first-generation antipsychotic, olanzapine and a first generation antipsychotic olanzapine and risperidone, risperidone and quetiapine olanzapine and aripiprazole, aripiprazole and a first generation antipsychotic, quetiapine and aripiprazole, blonanserin and a first generation antipsychotic, blonanserin and olanzapine, blonanserin and quetiapine.	Mean chlorpromazine equivalent = 635.0 mg/day
A +any antipsychotic 2015	Switch to antipsychotic monotherapy	Mean olanzapine equivalent = 32.9 mg/day	Half the patients were receiving either clozapine or a long-acting injectable antipsychotic as one of their 2 antipsychotics at baseline. No other information regarding which combinations were used.	Mean olanzapine equivalent = 41.2 mg/day

Footnotes
d - day

Appendix 6. Missing data

Study ID	Subgroup	Outcome	Data missing	
A +any antipsychotic 2015	Any antipsychotics in both groups	Clinical response: Global state - severity (CGI-S scale, high = bad)	No means and SDs reported.	Not added, no data
		Clinical response: 4. Global state - average improvement score (CGI-I scale, high = bad)		
		Mental state: Total score (PANSS scale, high = bad)		
		Mental state: Positive symptoms (PANSS scale, high = bad)		
		Mental state: Negative symptoms (PANSS scale, high = bad)		
		Adverse events: Movement disorders (AIMS, high = bad)		
		Adverse events: Movement disorders (SAS, high =bad)		
		Adverse events: Movement disorders (BAS, high= bad)		
B +aripiprazole 2008	Clozapine in both groups	Adverse events: Average weight gain (kg)	No SD, mean difference and CIs reported	Added using Revman calculator
		Clinical response: Global state - severity (CGI-I scale, high = bad)	SE reported not SD	Added using Revman calculator
		Clinical response: Global state - severity (CGI-S scale, high = bad)	SE reported as 0	Not added, not able to impute data
		Clinical response: 5. Global state - average functioning score (GAF scale, high = good	SE reported not SD	Added using Revman calculator
		Mental state: Total score (PANSS scale, high = bad)	SE reported as 0	Not added, not able to impute data
		Mental state: Positive symptoms (PANSS scale, high = bad)	SE reported not SD	Added using Revman calculator
		Mental state: Negative symptoms (PANSS scale, high = bad)		
		Quality of life: 1b. Average score (SWN, high = good)		
B +quet/risp 2009	Other atypical drugs in both groups	Adverse events: Average weight gain (kg)	No SD, P values reported	Not added, no similar mean, not

(Continued)

				able to impute data
		Mental state: Positive symptoms (PANSS scale, high = bad)		Data imputed from B +aripiprazole 2008
		Mental state: Negative symptoms (PANSS scale, high = bad)		
		Adverse events: Movement disorders (AIMS, high = bad)	No SD, mean reported in a graph	Not added - mean in Figure 2, no similar mean to impute
		Adverse events: Movement disorders (BAS, high = bad)		
		Adverse events: Movement disorders (SAS, high = bad)		
		Adverse events: Prolactin level (high = bad)	No SD, P values reported	Not added, no similar mean, not able to impute data
		Clinical response: Global state - severity (CGI-S scale, high = bad)		
		Mental state: Total score (PANSS scale, high = bad)		
		Quality of life (SWN, high = good)		
C +amisulpride 2008	Clozapine in both groups	Adverse events: Prolactin level (high = bad)	No SD, no other data	Not added - 2 combination groups with different doses, no similar means, not able to impute data
		Clinical response: Global state - severity (CGI-S scale, high = bad)		
		Clinical response: Global state (GAF scale, high = good)		
		Mental state: Depressive symptoms (MADRS scale, high = bad)		
		Mental state: Total score (BPRS scale, high = bad)		
C +aripiprazole 2007b	Typicals in both groups	Clinical response: Global state - severity (CGI-S scale, high = bad)	No SD, no other data	Data imputed from C +fluphendec 2009
		Mental state: Total score (BPRS scale, high = bad)		Data imputed from C +aripiprazole 2008
		Mental state: Negative symptoms (SANS scale, high = bad)		
C +aripiprazole 2008	Clozapine in both groups	Adverse events: Movement disorders (UKU, high = bad)	No means and SDs reported	Not added, no data
C +aripiprazole 2013b	Other atypical drugs in both groups	Mental state: Total score (PANSS scale, high = bad)	SE reported not SD	Added using Revman calculator
		Mental state: positive symptoms (PANSS scale, high = bad)		

(Continued)

		Mental state: Negative symptoms (PANSS scale, high = bad)		
		Adverse events: Movement disorders (ESRS, high = bad)		
C +aripiprazole 2015b	Other atypical drugs in both groups	Mental state: Total score (BPRS scale, high = bad)	No means and SDs reported.	Not added, no data
		Adverse events: Movement disorders (SAS, high = bad)		
		Adverse events: Movement disorders (BAS, high = bad)		
		Adverse events: Prolactin level (high = bad)		
C +aripiprazole 2015c	Other atypical drugs in both groups	Mental state: Total score (PANSS scale, high=bad)	Reported in a graph	Measured from figure 4
		Mental state: Positive symptoms (PANSS scale, high = bad)		
		Mental state: Negative symptoms (PANSS scale, high = bad)		
		Adverse events: Prolactin level (high = bad)		Measured from figure 2
C +aripiprazole 2016	Other atypical drugs in both groups	Adverse event: Movement disorders - Any	Reported as percentage not as absolute value	Added using excel 2011
		Adverse events: Prolactin level (high = bad)	Median and quartile reported not median and SD.	Not able to impute
C +CPZ 1989	Clozapine in both groups	Mental state: Total score (BPRS scale, high = bad)	SE reported not SD	Added using Revman calculator
C +levomepromazine 2004	Typicals in both groups	Mental state: Avarage score (BPRS scale, high = bad)	Reported in a graph	Measured from Figure 1
		Mental state: Positive symptoms (BPRS scale, high = bad)		
		Mental state: Negative symptoms (BPRS scale, high = bad)		
C +pimozide 2013	Clozapine in both groups	Mental state: Total score (BPRS scale, high=bad)	SE reported not SD	Added using Revman calculator
		Clinical response: Global state - severity (CGI-S scale, high=bad)		
		Clinical response: Global state - severity (CGI-I scale, low = bad)		

(Continued)

		Mental state: Negative symptoms (SANS scale, high = bad)		
C +risperidone 2005	Clozapine in both groups	Mental state: Total score (PANSS scale, high = bad)	SE reported not SD	Added using Revman calculator
		Mental state: Positive symptoms (PANSS scale, high = bad)		
		Mental state: Negative symptoms (PANSS scale, high = bad)		
		Clinical response: Global state - severity (CGI-S scale, high = bad)		
		Clinical response: Global state (GAF scale, high = good)		
		Quality of life (QLS high = good)		
		Adverse events: Movement disorders (AIMS, high = bad)		
		Adverse events: Movement disorders (SAS, high = bad)		
		Adverse events: Movement disorders (BAS, high = bad)		
		Adverse events: Movement disorders (UKU, high = bad)		
C +risperidone 2005b	Clozapine in both groups	Mental state: Total score (BPRS scale, high = bad)	No SD, no other data	Data imputed from C +aripiprazole 2008
		Mental state: Positive symptoms (BPRS scale, high = bad)		Data imputed from B +risperidone 2010
		Mental state: Negative symptoms (SANS scale, high = bad)		Data imputed from C +fluphendec 2009
		Adverse events: Movement disorders (SAS, high = bad)	No SD, mean in a graph	Not added, mean in Figure 4, no similar mean to impute
C +risperidone 2007	Clozapine in both groups	Adverse events: Prolactin level (high = bad)	No SD, no other data	Not added, no similar mean, not able to impute data
C +sertindole 2006	Clozapine in both groups	Mental state: Total score (PANSS scale, high = bad)	No SD, CI's reported	Added using Revman calculator
		Mental state: Positive symptoms (PANSS scale, high = bad)		

(Continued)

		Mental state: Negative symptoms (PANSS scale, high = bad)		
		Clinical response: Global state (GAF scale, high = good)		
		Clinical response: Global state - improvement (CGI-I scale, high = bad)		Not added - means reported as 0 and no SD, CI intervals -1 to 0
		Clinical response: Global state - severity (CGI-S scale, high = bad)		Not added - means reported as 0 and no SD, CI intervals 0 to 0
		Adverse events: Average weight gain (kg)		Added using Revman calculator
C +sulpiride 2003	Clozapine in both groups	Mental state: Total score (BPRS scale, high = bad)	No SD, no other data	Data imputed from C +pipotiazine 2000
		Mental state: Negative symptoms (SANS scale, high = bad)		Data imputed from C +pipotiazine 2000
		Mental state: Negative symptoms (SAPS scale, high = bad)		Not added, no similar mean, not able to impute data
C +sulpiride 2013	Other atypical drugs in both groups	Clinical Response: Not clinically improved	Reported as percentage not as absolute value	Added using excel 2011

Footnotes

AIMS - Abnormal Involuntary Movement Scale.
BAS - Barnes Akathisia Scale.
BPRS - Brief Psychiatric Rating Scale.
CGI-I - Clinical Global Impression - Improvement.
CGI-S - Clinical Global Impression - Severity
CI - confidence interval.
ESRS - Extrapyramidal Symptom Rating Scale.
GAF - Global Assessment of Functioning Scale.
MADRS - Montgomery–Åsberg Depression Rating Scale.
PANSS - Positive and Negative Syndrome Scale.
QLS - Quality of Life Scale.
SANS - Scale for the Assessment of Negative Symptoms.
SAPS - Scale for the Assessment of Positive Symptoms.
SAS - Simpson Angus Scale.
SD - standard deviation.
SE- standard error.
SWN - Subjective Well Being under Neuroleptics.
UKU - Udvalg for Kliniske Undersøgelser.

Appendix 7. Skewed data

Study ID	Subgroup	Outcome	MONOTHERAPY			COMBINATION		
			Mean	SD	N	Mean	SD	N
B +aripiprazole 2011	Clozapine in both groups	Mental state: Positive symptoms (SAPS scale, high = bad)	3.6	7.6	14	13.4	5.7	17
		Mental state: Positive symptoms (SANS scale, high = bad)	25.1	13.7	14	34.9	10.9	17
B +risperidone 2010	Clozapine in both groups	Adverse events: Movement disorders (BAS, high = bad)	0.7	1.6	25	0.9	2.1	28
		Adverse events: Movement disorders (AIMS, high = bad)	3.5	5.5	25	2.2	2.8	28
		Adverse events: Movement disorders (SAS, high = bad)	1.8	3.4	25	1.8	2.5	28
B +ziprasidone 2014	Clozapine in both groups	Mental state: positive symptoms (PANSS scale, high = bad)	14.4	4.8	20	11.7	3.1	20
		Mental state: Negative symptoms (PANSS scale, high = bad)	15.3	5.9	20	19.5	3.9	20
C +aripiprazole 2007b	Typicals in both groups	Adverse events: Movement disorders (BAS, high = bad)	0.1	0.2	26	0.1	0.1	28
		Adverse events: Movement disorders (SAS, high = bad)	3	2.5	26	3	2.9	28
		Adverse events: Prolactin level (high = bad)	25	30	26	95	40	28
C +aripiprazole 2012	Clozapine in both groups	Adverse events: Movement disorders (UKU, high = bad)	5.33	3.38	18	5.5	3.25	18
		Mental state: positive symptoms (PANSS scale, high = bad)	10.7	5.7	18	7.8	3.4	18
C +aripiprazole 2013b	Other atypical drugs in both groups	Mental state: Total score (PANSS scale, high = bad)	54	12.04	17	53.78	12.9	18

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		Mental state: positive symptoms (PANSS scale, high = bad)	12.47	3.63	17	12.33	2.97	18
		Mental state: Negative symptoms (PANSS scale, high = bad)	14.71	4	17	15.17	4.58	18
		Adverse events: Movement disorders (ESRS, high = bad)	8.53	9.73	17	8.67	9.72	18
C +aripiprazole 2014	Other atypical drugs in both groups	Adverse events: Prolactin level (high = bad)	20.98	16.34	59	94.1	64.84	57
C +aripiprazole 2015	Other atypical drugs in both groups	Mental state: Total score (PANSS scale, high = bad)	49.28	11.49	89	51.23	11.91	30
		Adverse events: Movement disorders (SAS, high = bad)	1.01	1.38	89	1.26	1.48	30
		Adverse events: Movement disorders (BAS, high = bad)	0.26	0.58	89	0.23	0.5	30
		Adverse events: Prolactin level (high = bad)	32.91	28.93	89	87.72	57.24	30
C +aripiprazole 2015b	Other atypical drugs in both groups	Mental state: Positive symptoms (BPRS scale, high = bad)	9.53	5.317	15	7.15	2.544	13
		Adverse events: Movement disorders (SAS, high = bad)	3	1.732	15	3.62	1.387	13
		Adverse events: Prolactin level (high = bad)	55.427	558.938	15	2170.46	1405.217	13
C +aripiprazole 2015c	Other atypical drugs in both groups	Mental state: Total score (PANSS scale, high = bad)	44	11	54	49	8	53
		Mental state: Positive symptoms (PANSS scale, high = bad)	10	3	54	11	4	53
		Mental state: Negative symptoms (PANSS scale, high = bad)	11	4	54	15	4	53
		Adverse events: Prolactin level (high = bad)	500	430	54	2000	1430	53

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C +aripiprazole 2016	Other atypical drugs in both groups	Mental state: Negative symptoms (PANSS scale, high = bad)	16.2	5.3	30	14.4	3.8	30
C +clozapine 2013	Other atypical drugs in both groups	Mental state: Total score (PANSS scale, high = bad)	51	16	25	52.96	14.39	25
		Mental state: Negative symptoms (PANSS scale, high = bad)	10.84	4.24	25	13.56	5.08	25
C +haloperidol 2010	Other atypical drugs in both groups	Adverse events: Movement disorders (BAS, high = bad)	0.87	1.61	46	0.9	1.43	42
		Adverse events: Movement disorders (AIMS, high = bad)	0.33	0.67	46	0.19	0.77	42
		Adverse events: Movement disorders (SAS, high = bad)	1.09	1.74	46	2.31	2.94	42
		Adverse events: Prolactin level (high = bad)	55.47	64.91	28	83.88	52.65	27
		Clinical response: Global state - severity (GAF scale, high = good)	21	12.9	46	20.1	13.6	42
C +olan/risp 2014	Other atypical drugs in both groups	Adverse events: Prolactin level (high = bad)	119.68	68.04	25	98.3	88.25	25
C +pipotiazine 2000	Clozapine in both groups	Adverse events: Movement disorders (TESS, high = bad)	4.9	5	26	5	4.9	24
C +pimozide 2013	Clozapine in both groups	Clinical response: Global state - severity (CGI-S scale, high = bad)	3.9	1.87	14	3.9	2.99	14
		Clinical response: Global state - severity (CGI-I scale, low = bad)	3.4	1.87	14	2.8	3.74	14
		Mental state: Negative symptoms (SANS scale, high = bad)	37.3	22.08	14	36.3	22.8	14
C +risperidone 2005	Clozapine in both groups	Clinical response: Global state - severity (CGI-S scale, high = bad)	4.3	4.48	16	4	0.4864	14

(Continued)

		Adverse events: Movement disorders (BAS, high = bad)	0.18	0.6	16	0.72	0.5987	14
		Adverse events: Movement disorders (AIMS, high = bad)	1.3	0.88	16	1	0.8606	14
		Adverse events: Movement disorders (UKU, high = bad)	0.7	0.36	16	0.2	0.3742	14
C +risperidone 2006	Clozapine in both groups	Adverse events: Movement disorders (BAS, high = bad)	0.5	0.7	32	0.4	0.8	33
		Adverse events: Movement disorders (ESRS, high = bad)	9.3	6.9	32	7.8	7	32
C +risperidone 2007	Clozapine in both groups	Adverse events: Movement disorders (BAS, high = bad)	0.4	0.7	11	0.3	0.5	13
		Adverse events: Movement disorders (AIMS, high = bad)	0.1	0.3	11	1	1.7	11
		Adverse events: Movement disorders (SAS, high = bad)	3.7	2.9	11	4.9	3.9	13
C +sulpiride 1999	Clozapine in both groups	Adverse events: Movement disorders (TESS, high = bad)	2.52	3.46	50	2.6	3.87	50
C +sulpiride 1999c	Clozapine in both groups	Mental state: Negative symptoms (SANS scale, high = bad)	23.6	14.3	29	28.2	17.5	30
		Adverse events: Movement disorders (TESS, high = bad)	3.4	2.5	30	2.9	2.3	20
C +sulpiride 2004	Other atypical drugs in both groups	Adverse events: Movement disorders (BAS, high = bad)	1	1.2	9	4.6	3.2	8
		Adverse events: Movement disorders (SAS, high = bad)	3.4	2.4	9	8	4.9	8
C +sulpiride 2013	Other atypical drugs in both groups	Adverse events: Prolactin level (high = bad)	52.7	58.2	29	59	69	31

Footnotes

AIMS - Abnormal Involuntary Movement Scale.
BAS - Barnes Akathisia Scale.
BPRS - Brief Psychiatric Rating Scale.
CGI-I - Clinical Global Impression - Improvement.
CGI-S - Clinical Global Impression - Severity.
ESRS - Extrapyramidal Symptom Rating Scale.
GAF - Global Assessment of Functioning Scale.
PANSS - Positive and Negative Syndrome Scale.
SANS - Scale for the Assessment of Negative Symptoms.
SAPS - Scale for the Assessment of Positive Symptoms.
SAS - Simpson Angus Scale.
SD - Standard deviation.
TESS - Treatment Emergent Symptom Scale.
UKU - Udvalg for Kliniske Undersøgelser.

WHAT'S NEW

Date	Event	Description
18 September 2017	Amended	We have made several amendments to the data and text of the review since publication. These changes have not substantively altered the overall conclusions of this review • Updated and corrected data extraction from C +perphenazine 1976, a Japanese trial. This changed the results for the outcome 'clinical response: not clinically improved' for the subgroup 'typical antipsychotics in both groups'. • Decided to not pool the data of the outcome 'relapse' due to high heterogeneity. • Amended Summary of findings for the main comparison • Separated endpoint data from change data. (see Differences between protocol and review). • Minor changes to PRISMA, conclusions and discussion sections. • Completed meta-regression for the primary outcome to investigate heterogeneity (see Differences between protocol and review).

HISTORY

Protocol first published: Issue 2, 2011
Review first published: Issue 6, 2017

Date	Event	Description
8 May 2017	New citation required but conclusions have not changed	Review fully updated with new data from search update. New results did not alter the overall conclusions of the review.
29 June 2016	New search has been performed	Results of update search added to review, minor changes to discussion and conclusions.
25 January 2016	Amended	Search updated and 1344 references were sent to the review authors for screening.

CONTRIBUTIONS OF AUTHORS

Javier Ortiz-Orendain - selection of studies, data extraction, 'Summary of findings' table, completion of report (2016).

Santiago Castiello - selection of studies, data extraction, 'Summary of findings' table, completion of report (2016).

Luis Enrique Colunga - referee for disagreement, 'Summary of findings' table, completion of report (2016).

Yue Hu - translation and data extraction of the Chinese papers.

Nicola Mayaan - protocol writing, selection of studies, data extraction, 'Summary of findings' table, completion of report (2012).

Clive Adams - protocol writing, completion of reports (2012, 2016).

DECLARATIONS OF INTEREST

Javier Ortiz-Orendain – participated in clinical trials sponsored by drug companies but received no payment for his contribution.

Santiago Castiello-de Obeso - none known.

Luis Enrique Colunga-Lozano - none known.

Yue Hu - works for Systematic Review Solutions Ltd, a company that carries out systematic reviews.

Nicola Mayaan - worked for Enhance Reviews Ltd during the preparation of this review, a company that carried out systematic reviews mostly for the public sector. Now works for Cochrane Respose.

Clive Adams - none known.

SOURCES OF SUPPORT

Internal sources

- University of Nottingham, UK.

External sources

- NIHR Programme Grant, UK.

  NIHR Programme Grant, 2010 (10/401/15)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The background was updated with more up-to-date references since the protocol publication in 2011.

We had planned to exclude studies that were quasi-randomised. However, of 62 trials analysed, only 18 reported an adequate generation of allocation sequence. Certainly, in two studies (B +sulpiride 1996; C +fluphen dec 2009) sequence generation was a quasi-randomised method (which we rated as having a high risk of bias), and three studies (C +CPZ 1999; C +sulpiride 1999; C +sulpiride 1999b) also posed a high risk of bias as they randomised according to hospital admission order or time. In all remaining studies, however, the method of assignment was unclear and we could not be sure these too had not used some form of quasi-random method. After debate, we decided not to specifically exclude the five studies named above as this could penalise authors for clarity and unfairly emphasise the findings of trials where methods of allocation were not well described. We do not think we were biased by the knowledge of results, and in no case did inclusion of the five trials materially alter the findings.

The order of the primary outcomes was changed because we consider 'Clinical Response' more relevant for patients (consumers), the general public, administrators and policy makers than 'Leaving the study early.' We also changed wording from clinically significant to clinically important, and clarified the 'Summary of findings' outcomes 'adverse effects' and 'quality of life' need to be clinically important data - as now specified as necessary by Cochrane Schizophrenia for all 'summary of findings' outcomes.

We planned to report data on subgroups of people in the same clinical state, stage, and with similar problems. However, most studies included participants with chronic schizophrenia, and we decided instead to present data in the analyses grouped by the type of antipsychotic used: trials with clozapine in both the monotherapy arm and in the combination arm of the trial, trials with other atypical drugs in both the monotherapy and combination arms, trials with typical antipsychotic drugs in both arms, or any antipsychotics in both groups, in order to facilitate subgroup analyses.

Due to a high heterogeneity in the outcome 'No clinically important response', we made a meta-regression with the random effect described by DerSimonian and Laird (DerSimonian 1986) to assess two potential effect modifiers: year of publication and Chinese studies. A meta-regression is similar to a simple regression but it consider different weights of studies depending on their inverse variance of each (Higgins 2011). We used the function 'rma.uni()' in the package 'metafor', for The R Project for Statistical Computing program.

Originally we had decided to use change data and baseline data in the same analysis, but after debate, we decided to present endpoint data and change data separately because we considered it problematic and full of assumptions that we were not comfortably taking.

One of the included trials (C +aripiprazole 2015b), was found by methods not reported in the protocol; this trial was found in an Internet search while working on one of the included studies (C +aripiprazole 2015).

We decided to establish an appendix 'Checklist to aid consistency and reproducibility of GRADE assessments' (Meader 2014) in order to aid with the standardisation of the 'Summary of findings' tables (Appendix 1).

INDEX TERMS

Medical Subject Headings (MeSH)

Antipsychotic Agents [*therapeutic use]; Clozapine [therapeutic use]; Drug Therapy, Combination; Patient Dropouts [statistics & numerical data]; Quality of Life; Randomized Controlled Trials as Topic; Recurrence; Schizophrenia [*drug therapy]; Treatment Outcome

MeSH check words

Humans