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Acetylsalicylic acid (aspirin) for schizophrenia (Review)

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[Intervention Review]

Acetylsalicylic acid (aspirin) for schizophrenia

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ABSTRACT

Background

Schizophrenia is a serious chronic mental illness affecting an estimated 21 million people worldwide and there is increasing evidence linking inflammation in the brain to the pathophysiology of schizophrenia. Antipsychotic drugs are the conventional treatment for people with schizophrenia but are not always fully effective. Acetylsalicylic acid (aspirin) is a non-steroidal anti-inflammatory drug (NSAID) with properties that inhibit the proinflammatory status of the brain. Using aspirin as an adjunct (add-on) treatment to antipsychotics or as a stand-alone treatment could be a novel, relatively inexpensive option for people with schizophrenia.

Objectives

To review the effects of acetylsalicylic acid (aspirin) as adjunct (add-on) or as stand-alone treatment for people with schizophrenia.

Search methods

We searched the Cochrane Schizophrenia Group's Trials Register (last search 8 March 2018) which is based on regular searches of MEDLINE, Embase, PubMed, CINAHL, BIOSIS, AMED, PsycINFO and registries of Clinical Trials. There are no language, date, document type, or publication status limitations for inclusion of records in the register.

Selection criteria

Randomised clinical trials focusing on aspirin for people with schizophrenia.

Data collection and analysis

We extracted data independently. For binary outcomes, we calculated risk ratio (RR) and its 95% confidence interval (CI), on an intention-to-treat (ITT) basis. For continuous data, we estimated the mean difference (MD) between groups and its 95% CI. We employed a fixed-effect model for analyses. We assessed risk of bias for included studies and created a 'Summary of findings' table using GRADE.

Main results

We included two studies, both comparing the effects of adding aspirin to standard antipsychotic treatment with adding placebo to standard antipsychotic treatment. We were hoping to find high-quality data for seven main outcomes of importance: clinically important change in global state, mental state, cognitive functioning and quality of life, numbers leaving the study early, incidence of gastrointestinal adverse events and hospital admission. Clinically important change data were not reported. Global state data were

reported by one study as 'unspecified problem necessitating change in dose or type of antipsychotics'; there was no clear difference between treatment groups for this outcome (RR 0.75, 95% CI 0.30 to 1.88; studies = 1; participants = 70; very low-quality evidence). Both trials measured mental state using the Positive and Negative Symptom Scale (PANSS), and mean total PANSS endpoint scores favoured the adjunct aspirin group in the medium term (MD -6.56, 95% CI -12.04 to -1.08; studies = 2; participants = 130; very low-quality evidence). Less than 10% of each group's participants left the studies early (for any reason) and by around three months there was no clear difference between numbers leaving early from the aspirin group compared to numbers leaving early from the placebo group suggesting aspirin is acceptable (RR 1.12, 95% CI 0.40 to 3.14; studies = 2; participants = 130; very low-quality evidence). There was some gastric upset in both groups but rates were not clearly different between the treatment groups (RR 1.03, 95% CI 0.55 to 1.94; studies = 1; participants = 70; very low-quality evidence). We are unclear if 'change in hospital status' is an unfavourable outcome or not as one study reported equivocal data (RR 0.56, 95% CI 0.05 to 5.90; studies = 1; participants = 70; very low-quality evidence). It should be noted that all the above results were based on data of very low-quality and were difficult to interpret for clinicians or patients, and that the two studies, completed in the last decade, failed to report any usable outcomes on cognitive functioning or quality of life.

Authors' conclusions

We highlighted the evidence that some pioneering researchers feel this question is important enough to merit testing in randomised trials. However, we also highlighted that the evidence produced from these trials was weak and inconclusive. It was impossible to draw clear conclusions on the therapeutic value of aspirin for schizophrenia from these short, small and limited trials.

PLAIN LANGUAGE SUMMARY

Aspirin as an add-on treatment to antipsychotics for people schizophrenia

Background

Schizophrenia is a serious mental illness that affects around 21 million people worldwide. The symptoms of schizophrenia are typically classified into positive (e.g. hallucinations and delusional thoughts), negative (e.g. withdrawal and difficulty with social interaction) and cognitive (e.g. poor attention and restricted working memory) groups. These symptoms cause distortions in an individual's behaviour, thinking, emotions, sense of self and perception. Usually, antipsychotic medicines are used for treating the symptoms of schizophrenia.

In recent years, inflammation (swelling) in a person's brain was linked to the symptoms that accompany schizophrenia. Aspirin is an affordable medicine which acts against inflammation and, therefore, it is thought it could help reduce the symptoms of schizophrenia. In this review, we looked at the effects of using aspirin as an add-on treatment for people with schizophrenia.

Study characteristics

After searching Cochrane Schizophrenia's database in March 2018 and assessing the search results, we included one randomised controlled trial (clinical studies where people are randomly put into one of two or more treatment groups) from the Netherlands (70 participants) and one from Iran (60 participants). Both trials used aspirin as an add-on treatment to standard antipsychotic medication and compared it with placebo (a dummy treatment), also as an add-on to standard treatment.

Key results

Participants receiving aspirin had slightly better results for their mental state, which was measured with the Positive and Negative Symptom Scale (PANSS). For side effects related to stomach problems, there seemed to be no clear difference between the groups. The same applied to changes in hospital status and leaving the study early. However, all these results were based on analyses of very poor data and graded as very low-quality evidence. No trial gave usable information on cognitive functioning or quality of life.

Quality of the evidence

This review was based on results from only two small trials, which made it impossible to say whether aspirin would be a good treatment option for people with schizophrenia. More information from the trials that are underway could strengthen the results of this analysis.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Aspirin + antipsychotics compared to placebo + antipsychotics for people with schizophrenia

Patient or population: people with schizophrenia
Setting: inpatients and outpatients
Intervention: aspirin + antipsychotics
Comparison: placebo + antipsychotics

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo + antipsychotics	Risk with aspirin + antipsychotics				
Global state: any change in global state - unspecified problem necessitating change in dose or type of antipsychotics - medium term	243 per 1000	182 per 1000 (73 to 457)	**RR 0.75** (0.30 to 1.88)	70 (1 RCT)	⊕◯◯◯ **Very low**[a,b,c]	Data for our predefined outcome, clinically important change in global state, were not reported. Data on global state outcomes were very sparse. This was the only outcome in the global state domain
Mental state: general - mean endpoint score (PANSS total, high = poor) - medium term	-	MD in the intervention group was 6.56 lower (12.04 lower to 1.08 lower)	-	130 (2 RCTs)	⊕◯◯◯ **Very low**[b,c,d]	Data for our predefined outcome, clinically important change in mental state were not reported
Cognitive functioning: clinically important change in cognitive functioning	See comment	See comment	-	-	-	Unable to retrieve usable data on this outcome.

Leaving the study early: short-term - for any reason	105 per 1000	118 per 1000 (42 to 331)	**RR 1.12** (0.40 to 3.14)	130 (2 RCTs)	⊕○○○ **Very low**[a,b]	-
Adverse events: gastrointestinal - dyspeptic symptoms - self-assessed as at least 'moderate'	405 per 1000	418 per 1000 (223 to 786)	**RR 1.03** (0.55 to 1.94)	70 (1 RCT)	⊕○○○ **Very low**[a,b]	Combined data for self-assessed 'moderate', 'serious' and 'very serious' symptoms. According to the study's authors, there were no complaints requiring medical attention. Data on adverse events were sparse and reported only in 1 study
Quality of life: clinically important change	-	-	-	-	-	We were unable to retrieve any outcomes related to quality of life
Service use: change in hospital status - any change	54 per 1000	30 per 1000 (3 to 319)	**RR 0.56** (0.05 to 5.90)	70 (1 RCT)	⊕○○○ **Very low**[a,b,c]	Data for our predefined outcome 'hospital admission' were not reported

*__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; **MD:** mean difference; **PANSS:** Positive and Negative Symptom Scale; **RCT:** randomised controlled trial; **RR:** risk 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

[a]Imprecision: downgraded two levels for small sample size or wide confidence intervals, or both.

[b]Publication bias: downgraded one level since a number of unpublished trials were identified in search. Number of trials included for this outcome was very low.
[c]Indirectness: downgraded one level as outcomes were proxy measures of what had been prestipulated within the original protocol for this review.
[d]Imprecision: downgraded one level for small sample size.

BACKGROUND

Description of the condition

Schizophrenia is a chronic serious mental illness affecting an estimated 21 million people worldwide (WHO 2018). Individuals are typically diagnosed with schizophrenia following assessment of their behaviour to determine their mental state and to rule out other possible causes such as substance abuse or another medical condition (Barbato 1998). The symptoms of schizophrenia are typically classified into positive, negative and cognitive groups. Positive symptoms are characteristic of schizophrenia and include hallucinations and delusional thoughts, while negative symptoms include diminished motivation, withdrawal and difficulty with social interaction (WHO 2018). Cognitive symptoms include limited executive functioning, poor attention and restricted working memory which results in an inability to organise simple tasks and work sequentially and effectively (Simpson 2010). These symptoms cause distortions in an individual's behaviour, thinking, emotions, sense of self and perception (WHO 2018).

Recovery from the symptoms of schizophrenia varies between individuals. Research has shown that 45% of people with schizophrenia will recover after one or more episodes, 35% will experience a mixed pattern of remission and relapse, while a further 20% will present unremitting symptoms and disability (Barbato 1998). Individuals diagnosed with schizophrenia frequently experience stigma and discrimination, and are estimated to die 12 to 15 years earlier than the mean population (van Os 2009). The specific origins of schizophrenia have yet to be identified; however, several possible causes have been recognised. These include several neurotransmitter dysfunctions involving dopaminergic, glutamatergic and gamma-aminobutyric acid (GABA)ergic signalling, indications of disturbances in neuron myelination, impairments to the functioning of the brain's prefrontal cortex and increasing evidence linking inflammation in the brain to the pathophysiology of schizophrenia (Kroken 2014; Smyth 2013).

Description of the intervention

Antipsychotic drugs are the mainstay of treatment for schizophrenia, and include the conventional 'typical' antipsychotics, chlorpromazine, haloperidol, perphenazine and fluphenazine, and second-generation 'atypical' antipsychotics such as risperidone, aripiprazole, ziprasidone and olanzapine. Antipsychotics are primarily effective in the treatment of positive symptoms, but have demonstrated small effect sizes in the treatment of the cognitive symptoms of schizophrenia which are evident prior to the development of psychosis and often remain once the symptoms of psychosis have been treated (Kroken 2014).

Growing awareness of the role of inflammation in the development of schizophrenia has resulted in research to identify possible additional molecular therapeutic targets, including adjunctive treatment options involving non-steroidal anti-inflammatory drugs (NSAIDs) such as acetylsalicylic acid (aspirin) (Berk 2013). Aspirin is an inexpensive World Health Organization essential medicine that is commonly used as a treatment for mild to moderate pain and inflammation. In addition to its anti-inflammatory properties, aspirin contributes to the prevention of myocardial infarction, stroke and dementia, but is not widely used as a conventional treatment for schizophrenia. Aspirin is taken orally at varying doses depending on the condition being treated, with a typical dose of 0.3 g to 1 g repeated every four hours according to clinical needs, up to a maximum of 4 g daily (some inflammatory diseases may require a higher dose) (Reynolds 1982).

How the intervention might work

Anti-inflammatory agents such as aspirin possess properties which inhibit the proinflammatory status of the brain. Neuroinflammation triggers microglial activation resulting in the production of inflammatory molecules which include cytokines, phagocytotic cells/proteins and disruption of the blood-brain barrier (Kirkpatrick 2013). Blood serum levels of the cytokine interleukin (IL)-6 are raised for individuals experiencing a first episode of schizophrenia and those in acute relapse (Miller 2011). Stimulation of proinflammatory cytokines may activate pathways which play a role in the regulation of serotonin, glutamate and dopamine (Benros 2014), with interactions between the IL-6 and dopamine pathways noted (Girgis 2014).

Cyclooxygenase (COX) is a key enzyme in the biosynthesis of molecules such as prostaglandins and thromboxanes, which in turn modulate the production of inflammatory cytokines (Nitta 2013). Aspirin inhibits the production of the COX-1 enzyme and modifies the activity of COX-2, thereby interrupting the neurotoxic inflammatory cascade and suppressing the production of prostaglandins, thromboxanes and other inflammatory molecules including cytokines (Berk 2013; Laan 2008). Adverse effects caused by aspirin include gastric ulcers and bleeding.

Why it is important to do this review

Individuals with schizophrenia identified as having higher levels of inflammatory markers may benefit from the development of additional therapeutic targets, and this review investigated whether aspirin as an adjunctive treatment offers a beneficial treatment option in combination with antipsychotics. One meta-analysis investigated several anti-inflammatory agents (including celecoxib, davunetide, fatty acids, oestrogens, minocycline, N-acetylcysteine and aspirin) as adjunctive treatments for schizophrenia (Sommer 2014). This review focused on establishing whether aspirin is an effective intervention for the treatment of schizophrenia and included data from published randomised controlled trials.

OBJECTIVES

To review the effects of acetylsalicylic acid (aspirin) as adjunct (add-on) or as stand-alone treatment for people with schizophrenia.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials. If a trial was described as 'double-blind' but implied randomisation, we would have included such trials in a sensitivity analysis (see Sensitivity analysis). We excluded quasi-randomised studies, such as those allocating by alternate days of the week.

Types of participants

Adults aged 18 years or over with a diagnosis of schizophrenia or related disorders, including schizophreniform disorder, schizoaffective disorder and delusional disorder using any diagnostic criteria. We included trials where the majority (over 50%) of participants had a diagnosis of schizophrenia.

We aimed to ensure information contained in this review was as relevant to the current care of people with schizophrenia as possible. Where information was available, we clearly highlighted the current clinical state (acute, early postacute, partial remission, remission), stage of illness (prodromal, first episode, early illness, persistent) and whether the studies primarily focused on people with specific disorders (e.g. treatment-resistant illness or negative symptoms).

Types of interventions

1. Acetylsalicylic acid (aspirin)

Aspirin administered by any means of delivery or dose (adjunct or stand-alone treatment). We would have reported separate comparisons for when aspirin was used as part of an adjunct treatment and for when it was used as sole treatment.

2. Placebo

Active or inactive placebo treatments administered by any means of delivery or dose (adjunct or stand-alone treatment).

3. Any antipsychotic treatment (adjunct or stand-alone treatment)

Types of outcome measures

We divided all outcomes into short-term (up to eight weeks), medium term (eight weeks to six months) and long term (six months or longer).

We endeavoured to report binary outcomes recording clear and clinically meaningful degrees of change (e.g. global impression of much improved, or more than 50% improvement on a rating scale - as defined within the trials) before any others. Thereafter, we listed other binary outcomes and then those that were continuous. For outcomes such as 'clinically important change', 'any change' and 'relapse', we used the definition used by each of the trials. For valid scales, see Data extraction and management.

Primary outcomes

1. Global state

1.1 Clinically important change in global state (for example, at least 50% change in Clinical Global Impressions Scale (CGI)

2. Mental state

2.1 Clinically important change in mental state

3. Cognitive functioning

3.1 Clinically important change in cognitive functioning

Secondary outcomes

1. Global state

1.1 Any change in global state

1.2 Relapse

1.3 Average endpoint or change score on global state scale

2. Mental state

2.1 General symptoms.

2.1.1 Any change in mental state
2.1.2 Average endpoint or change score on general mental state scale

2.2 Specific symptoms - average endpoint or change score on specific symptoms scale

2.2.1 Positive symptoms (e.g. delusions, hallucinations).
2.2.2. Negative symptoms (e.g. avolition, blunted affect).
2.2.3. Mood (e.g. anxiety, depression).
2.2.4. Other psychotic symptoms (e.g. disorganised thought).

3. Cognitive functioning

3.1. General

3.1.1. Clinically important change in general cognitive functioning
3.1.2. Any change in general cognitive functioning
3.1.3. Average endpoint or change score on general cognitive functioning scale

3.2. Specific

3.2.1. Clinically important change in specific cognitive functioning
3.2.2. Any change in specific cognitive functioning.
3.2.3. Average endpoint or change score on specific cognitive functioning scale

4. Functioning

4.1. General functioning

4.1.1. Clinically important change in general functioning
4.1.2. Average endpoint in general functioning
4.1.3. Average endpoint or change score on general functioning scale

4.2. Specific functioning

4.2.1. Clinically important change in specific functioning
4.2.2. Any change in specific functioning.
4.2.3. Average endpoint or change score on specific functioning scale.

5. Behaviour

5.1. General behaviour

5.1.1. Clinically important change in general behaviour
5.1.2. Any change in general behaviour.
5.1.3. Average endpoint or change score on general behaviour scale

5.2. Specific behaviour

5.2.1. Clinically important change in specific behaviour
5.2.2. Any change in specific behaviour.
5.2.3. Average endpoint or change score on specific behaviour scale

6. Leaving the study early

6.1 Leaving the study early due to adverse effects

6.2 Leaving the study early for poor clinical effect

7. Adverse events

7.1 General adverse events (measured as scores or binary)

7.2 Specific adverse events (measured as scores or binary)

7.2.1 Allergic reactions.
7.2.2 Gastrointestinal (nausea, vomiting, diarrhoea, bleeding)
7.2.3 Weight gain.

8. Quality of life

8.1 Clinically important change in quality of life

8.2 Any change in quality of life measure

8.3 Average endpoint or change score on quality of life scale

9. Service use

9.1 Hospital admission

9.2 Days in hospital

9.3 Change in hospital status

10. Inflammation markers

10.1 C-reactive protein levels in blood plasma

10.2 Cytokine levels

11. Economic

11.1 Direct costs

11.2 Indirect costs

'Summary of findings' table

We used the GRADE approach to interpret findings (Schünemann 2011), GRADEpro GDT to export data from our review and Review Manager 2014 to create a 'Summary of findings' table. These tables provide 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. We selected the following main outcomes for inclusion in our 'Summary of findings' table: and preferred these to be for medium term (eight weeks to six months).

- Global state - clinically important change in global state.
- Mental state - clinically important change in mental state.
- Cognitive functioning - clinically important change in general cognitive functioning.
- Leaving the study early - for any reason.
- Adverse events - gastrointestinal (e.g. nausea, vomiting, diarrhoea).
- Quality of life - clinically important change in quality of life
- Service use - hospital admission.

If data were not available for these prespecified outcomes but were available for ones that were similar, we presented the closest outcome to the prespecified one in the table but took this into account when grading the finding.

Search methods for identification of studies

Electronic searches

Cochrane Schizophrenia Group's Study-Based Register of Trials

On 24 March 2016, 29 June 2017 and 8 March 2018, the Information Specialist searched this register using the following search strategy:
Acetylsalicylic Acid (Aspirin) in Intervention Field of STUDY
In such a study-based register, searching the major concept retrieves all the synonyms and relevant studies because all the studies have already been organised based on their interventions and linked to the relevant topics (Shokraneh 2017).
This register is compiled by systematic searches of major resources (MEDLINE, Embase, AMED, BIOSIS, CENTRAL, CINAHL, ClinicalTrials.Gov, PsycINFO, PubMed, and World Health Organization (WHO) ICTRP) and their monthly updates, ProQuest Dissertations and Theses A&I and its quarterly update, Chinese databases (CBM, CNKI and Wanfang) and their annual 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

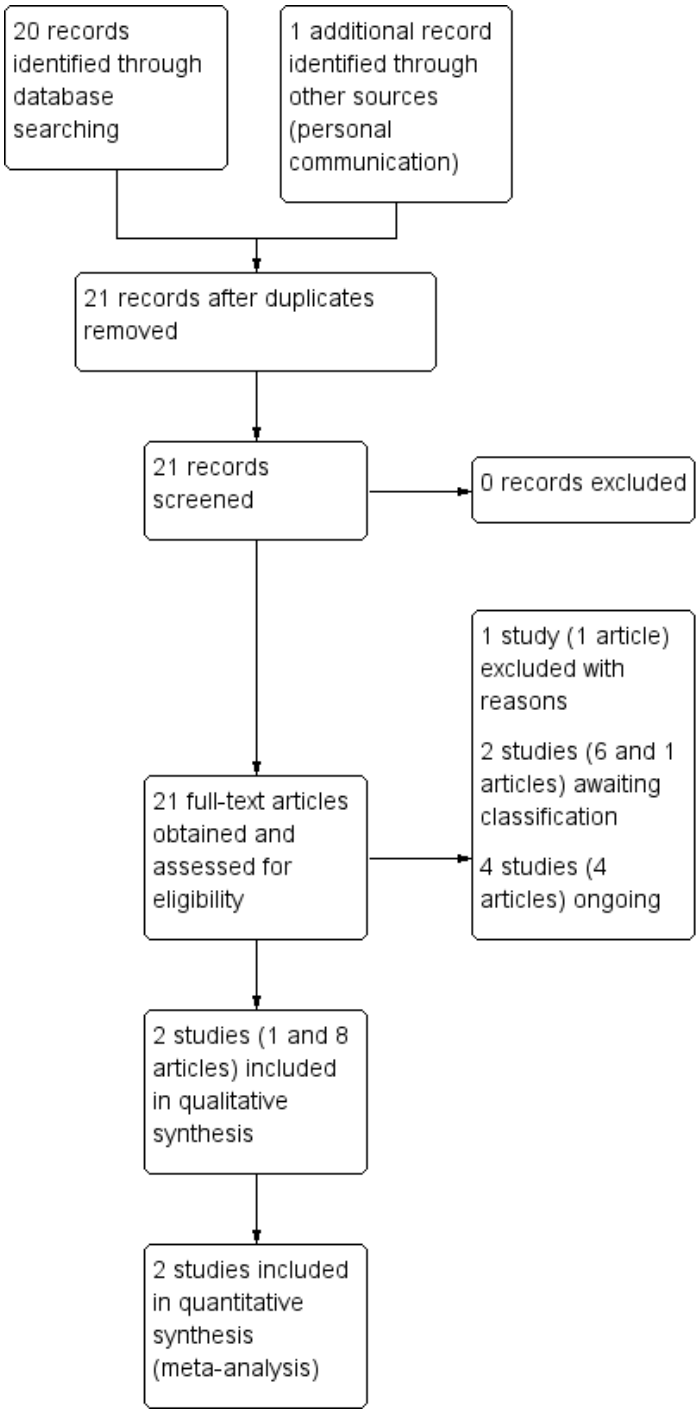
We contacted the first author of each included study for information regarding unpublished trials, but found no further trials.

Data collection and analysis

Selection of studies

For the 2016 search, Tracey Roberts (TR) independently inspected citations from the searches and identified relevant abstracts (see Acknowledgements). Two review authors (LS and JF) independently reinspected all to ensure reliability. There were no disputes, but we would have acquired the full report for more detailed scrutiny. TR obtained and inspected full reports of the abstracts meeting the review criteria. Three review authors (LS, EP and JF) independently reinspected these full reports to ensure reliable selection. For the 2017 and 2018 searches, three review authors (LS, EP and JF) independently inspected citations. We summarised trial selection in a PRISMA flow diagram (Figure 1).

Figure 1. Study flow diagram.



Data extraction and management

1. Extraction

The review authors (LS and EP) independently extracted data from the included studies. TR and one review author (LS) inputted the data and one review author (EP) checked it. Two review authors (LS and EP) would have discussed any disagreements. If needed, we contacted study authors through an open-ended request to obtain missing information or for clarification. Two review authors (LS and EP) received replies from Laan 2010. Furthermore, we contacted all authors of ongoing studies and studies awaiting assessment and discussed replies in the Results section (see 'Studies awaiting assessment' and 'Ongoing studies').

2. Management

2.1 Forms

We extracted data onto standard, simple forms.

2.2 Scale-derived data

We included continuous data from rating scales only if:

- the psychometric properties of the measuring instrument had been described in a peer-reviewed journal (Marshall 2000);
- the measuring instrument had not been written or modified by one of the trialists for that particular trial and
- the instrument had a global assessment of an area of functioning and not subscores which are not, in themselves, validated or shown to be reliable. However, there were exceptions, we included subscores from mental state scales measuring positive and negative symptoms of schizophrenia.

Ideally the measuring instrument should have been: 1. a self-report or 2. completed by an independent rater or relative (not the therapist). We realise that this is not often reported clearly and we noted if this was the case or not in Risk of bias in included studies and Characteristics of included studies table.

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. In contrast, calculation of change needs two assessments (baseline and endpoint), which can be difficult in unstable and difficult-to-measure conditions such as schizophrenia. We primarily used endpoint data, and only used change data if the former were not available. We combined endpoint and change data in the analysis as we aimed, wherever possible, to use the mean differences (MD) rather than standardised mean differences (SMD) throughout (Deeks 2011).

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.

For larger studies (more than 200 participants) and change data

We would have entered data from studies of at least 200 participants into the analysis irrespective of the following rules, because skewed data pose less of a problem in large studies. We also would have entered 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 determine whether such data are skewed or not. We would have presented and entered change data into statistical analyses.

For endpoint data from smaller studies (fewer than 200 participants)

- When a scale starts from the nite number zero, we subtracted the lowest possible value from the mean, and divide this by the standard deviation (SD). If this value is lower than 1, it strongly suggests a skew and we would have excluded these data. If this ratio is higher than 1 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 is larger than 2 we included these data, because skew is less likely (Altman 1996).
- 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

To facilitate comparison between trials, we intended, where possible, to convert variables that could 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 attempted to convert 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 PANSS (Kay 1986), this could be considered as a clinically significant response (Leucht 2005a; Leucht 2005b). 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 aspirin. Where keeping to this made it impossible to avoid outcome titles with clumsy double-negatives (e.g. 'Not unimproved'), we reported data where the left of the line indicated an unfavourable outcome for aspirin and made a note in the relevant graphs.

Assessment of risk of bias in included studies

Three review authors (LS, EP and TR) independently assessed risk of bias 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, in domains such as sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting.

Two review authors (LS and EP) made the final rating by consensus, with the involvement of a third review author (JF). Where there were inadequate details of randomisation and other characteristics of trials, two review authors (LS and EP) contacted authors of the studies to request further information. If disputes arose as to which category a trial was to be allocated, we resolved these by discussion.

We noted the level of risk of bias in the Risk of bias in included studies; 'Risk of bias' table; Figure 2; Figure 3; and Summary of findings for the main comparison.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

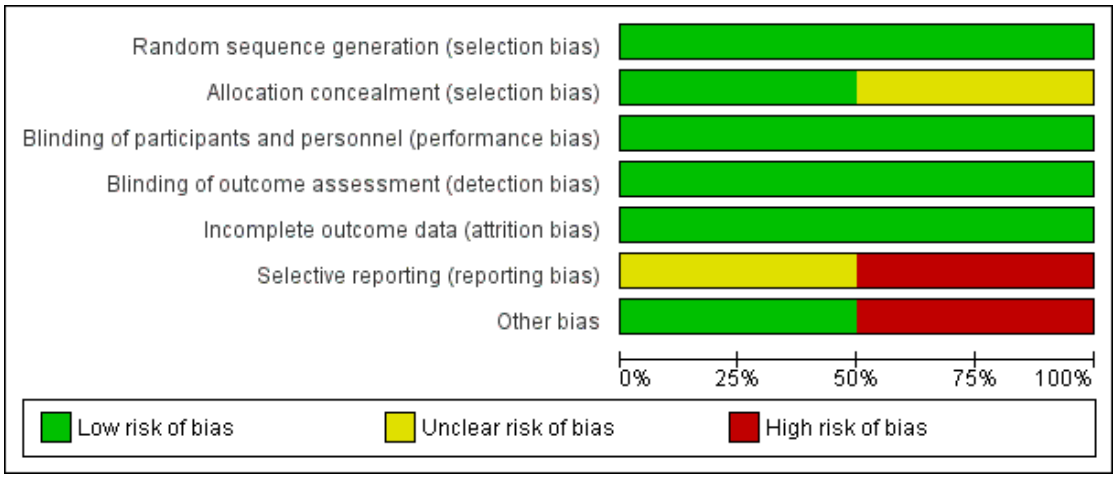
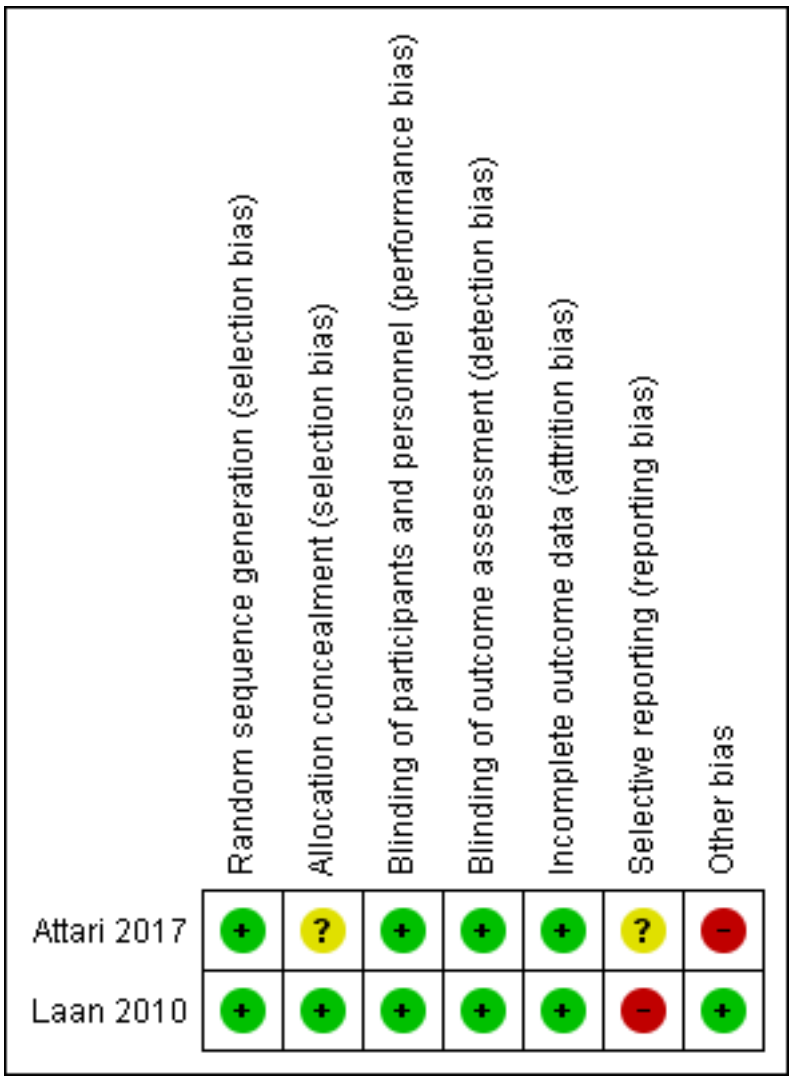


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



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 (SMD). However, if scales of very considerable similarity had been used, we would have presumed there was a small difference in measurement, and would have calculated 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. First, authors often fail to account for intraclass correlation in clustered studies, leading to a 'unit of analysis' error (Divine 1992), whereby P values are spuriously low, CIs unduly narrow and statistical significance overestimated. This causes type I errors (Bland 1997; Gulliford 1999).

Where clustering is not accounted for in primary studies, we would have presented data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. We planned to contact first authors of studies to obtain intraclass correlation coefficients (ICCs) for their clustered data and to adjust for this by using accepted methods (Gulliford 1999).

Where clustering had been incorporated into the analysis of primary studies, we would have presented these data as if from a non-cluster randomised study, but adjusted for the clustering effect.

We 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 (m) and the ICC [design effect = 1 + (m - 1) × ICC] (Donner 2002). If the ICC was not reported, we would have assumed it to be 0.1 (Ukoumunne 1999).

If cluster studies had 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. This 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 washout 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 would have 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 would have presented the additional treatment arms in comparisons. If data were binary, we would have simply added and combined within the two-by-two table. If data were continuous, we would have combined data following the formula in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). Where the additional treatment arms were not relevant, we would not have reproduced these data.

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. However, if more than 50% of those in one arm of a study were lost, but the total loss was less than 50%, we would have addressed this within the 'Summary of findings' table by downgrading quality. Finally, we would also have downgraded quality within the 'Summary of findings' table should loss have been 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 ITT analysis). Those leaving the study early were all assumed to have the same rates of negative outcome as those who completed, with the exception of the outcome of death and adverse effects. For these outcomes, we used the rate of those who stay in the study - in that particular arm of the trial - for those who did not. We planned, where possible, to undertake a sensitivity analysis testing how prone the primary outcomes were to change when data only from people who complete the study to that point were compared to the ITT analysis using the above assumptions.

3. Continuous

3.1 Attrition

Where attrition for a continuous outcome was between 0% and 50%, and data only from people who complete the study to that point were reported, we reproduced these.

3.2 Standard deviations

If SDs were not reported, we would have tried to obtain the missing values from the authors. If they were not available, where there were missing measures of variance for continuous data, but an exact standard error (SE) and CIs available for group means, and either P value or t value available for differences in mean, we could have calculated them according to the rules described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). When only the SE is reported, SDs are calculated by the formula SD = SE * square root (n). The *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b) presents detailed formulae for estimating SDs from P values, t or F values, CIs, ranges or other statistics. If these formulae did not apply, we

would have 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 have been to exclude a given study's outcome and thus to lose information. We nevertheless would have 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 consider 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. Therefore, we did not exclude studies based on the statistical approach used. However, we preferably would have used the more sophisticated approaches; that is, MMRM or multiple imputation to LOCF and we would only present completer analyses if some type of ITT data was 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 inspected all studies for clearly outlying people or situations which we had not predicted would arise. When such situations or participant groups arose, we would have discussed these in the text.

2. Methodological heterogeneity

We considered all included studies initially, without seeing comparison data, to judge methodological heterogeneity. We inspected all studies for clearly outlying methods which we had not predicted would arise. When such methodological outliers arose, we would have discussed these in the text.

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 statistic alongside the Chi^2 P value. The I^2 statistic provides an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of the I^2 statistic depends on: 1. magnitude and direction of effects and 2. strength of evidence for heterogeneity (e.g. value from Chi ^{2} test, or a CI for the I^2 statistic). We interpreted an I^2 estimate greater than or equal to around 50% accompanied by a statistically significant Chi^2 statistic as evidence of substantial levels of heterogeneity (*Cochrane Handbook for Systematic Reviews of Interventions*; Deeks 2011)). When there were substantial levels of heterogeneity, we noted these, and for primary outcomes, would have explored reasons for 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 10.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2011).

1. Protocol versus full study

We attempted to locate protocols of the included trials. If the protocol was available, we compared outcomes in the protocol with those in the published report. If the protocol was not available, we compared outcomes listed in the methods section of the trial report with the actually reported results.

2. Funnel plot

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 intend to use funnel plots for outcomes where there were 10 or fewer studies, or where all studies were of similar size. In other cases, where funnel plots were possible, we would have sought 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. However, there is a disadvantage to the

random-effects model. It puts added weight onto small studies which often are the most biased. Depending on the direction of effect these studies can either inflate or deflate the effect size. We used a fixed-effect model for analyses.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

1.1 Primary outcomes

There were not enough studies available to justify completing any subgroup analysis in this review.

1.2 Clinical state, stage or problem

We proposed to undertake this review and provide an overview of the effects of aspirin for people with schizophrenia in general. In addition, however, we intended to report data on subgroups of people in the same clinical state, stage and with similar problems.

2. Investigation of heterogeneity

We reported if inconsistency was high. First, we investigated whether data had been entered correctly. Second, if data were correct, we visually inspected the graph and successively removed studies outside of the company of the rest 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 have presented such data. If not, we would have pooled data and discussed the 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.

When unanticipated clinical or methodological heterogeneity were obvious we would have stated hypotheses regarding these for future reviews or versions of this review. We did not undertake analyses relating to these.

Sensitivity analysis

1. Implication of randomisation

We would have included trials in a sensitivity analysis if they were described in some way as to imply randomisation. For the primary outcomes, we would have included these studies and if there was no substantive difference when the implied randomised studies were added to those with better descriptions of randomisation, then we would have employed all 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 would have reported results and discussed them but continued to employ our assumption.

Where assumptions had to be made regarding missing SD data (see Dealing with missing data), we would have compared the findings on primary outcomes when we used our assumption compared with completer data only. We would have undertaken a sensitivity analysis testing 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 would have reported results and discussed them but continued to employ our assumption.

3. Risk of bias

We would have analysed the effects of excluding trials that were at high risk of bias across one or more of the domains of randomisation (Assessment of risk of bias in included studies) 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, then we would have included all relevant data from these trials in the analysis.

4. Imputed values

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

If there were substantial differences in the direction or precision of effect estimates in any of the sensitivity analyses listed above, we would not have pooled data from the removed trials with the other trials contributing to the outcome, but would have presented them separately.

5. Fixed-effect and random-effects models

We synthesised all data using a fixed-effect model; however, we also synthesised data for the primary outcome using a random-effects model to evaluate whether this altered the significance of the results. If there had been a difference, we would have noted this in the text.

RESULTS

Description of studies

For a substantive description of studies, see Characteristics of included studies and Characteristics of excluded studies tables.

Results of the search

In the original search, we found 20 records that were potentially relevant and gained one more through personal communication. We assessed all 21 full-text papers for eligibility. We then grouped these into 'studies' where several of the reports referred to the same trial (Figure 1). It was possible to include two studies (Attari 2017; Laan 2010; nine publications)

Included studies

The two studies investigated the same comparison (aspirin plus antipsychotics versus placebo plus antipsychotics).

1. Methods

Both studies had a randomised, controlled parallel design and used stratification before randomisation. Laan 2010 was double blind, while Attari 2017 was described as triple blind.

2. Length of trials

Both included in this review studies were conducted over the medium term (eight weeks to six months). Both studies also reported outcomes for the short term (up to eight weeks).

3. Participants

Both studies included men and women with Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) schizophrenia or schizophrenia spectrum disorder. All participants were receiving antipsychotics. Mean age and inclusion/exclusion criteria were similar in both studies. Combined baseline PANSS scores for all groups in Attari 2017 were higher (mean 131, SD 33) compared with Laan 2010 (mean 72, SD 10).

4. Setting

Laan 2010 was a multi-centre trial and included inpatients and outpatients based in 10 psychiatric hospitals throughout the Netherlands. Attari 2017 included people referred to a psychiatric hospital or emergency department in Iran. However, it was not reported whether these were inpatients or outpatients.

5. Study size

In total, both studies randomised 130 participants (60 in Attari 2017; 70 in Laan 2010).

6. Interventions

Both studies compared antipsychotics and adjunct aspirin with antipsychotics and placebo. Participants in both studies also received gastric protection.

Laan 2010 had two parallel arms. Participants in the experimental arm (33 at start of trial) received their regular daily antipsychotics, oral adjunct aspirin 1000 mg/day, and pantoprazole 40 mg/day for gastric protection. The control arm (37 at start of study) also received regular daily antipsychotics plus oral placebo and pantoprazole 40 mg/day for gastric protection. Olanzapine, clozapine and risperidone were described as the antipsychotics used by most of the participants.

Attari 2017 had three parallel arms, with 20 participants allocated to each arm. All participants received their regular antipsychotics in a dose equivalent to chlorpromazine 100 mg/day (35× risperidone, 18× olanzapine, 4× haloperidol, 3× chlorpromazine), and omeprazole 20 mg/day for gastric protection. In addition, participants in the first experimental arm received oral adjunct aspirin 325 mg/day, participants in the second experimental arm received oral adjunct aspirin 500 mg/day and participants in the control arm received an oral placebo tablet.

7. Outcomes

7.1 Outcome scales

The trials used a variety of scales to measure outcomes. Those reporting useable data are described below.

a. Positive and Negative Symptom Scale (PANSS)

The PANSS (Kay 1986) was developed from the BPRS and the Psychopathology Rating Scale. It is used to evaluate the positive, negative and general symptoms in schizophrenia. The scale has 30 items, and each item is rated on a 7-point scoring system varying from 'absent' (1) to 'extreme' (7). Higher scores indicate more pronounced symptomatology.

b. Likert scale for dyspeptic complaints

The 5-point Likert scale is an instrument to measure severity of gastrointestinal symptoms (Veldhuyzen Van Zanten 1993). It is comprised of eight questions. The self-reported symptoms can be rated from 'No problem' (1) to 'Very severe problem, markedly influences your daily activities and/or requires rest' (5). Laan 2010 used this scale to measure dyspeptic complaints. However, these events were reported as the binary outcomes 'moderate', 'serious' and 'very serious' dyspeptic symptoms, relating to 3 of the 5 endpoints of this scale.

8. Missing outcomes

These small studies failed to assess or report many outcomes that could have been of interest. We prespecified some outcomes we believe are important to measure in our protocol (Roberts 2016), for example, cognitive functioning and quality of life. Laan 2010 reported data for cognitive functioning but they were unusable; neither trial reported data for quality if life. We also had to use proxies for some important outcomes, for example, no trial directly reported 'clinically important changes' in global state so we used the reported outcome 'necessitating change in dose or type of antipsychotics'. Considering how inexpensive the intervention is, and how expensive the potential outcomes are, it is surprising that there is no reporting of economic costs.

9. Unused outcomes

We were unable to use outcome data on T_H1/T_H2 cytokine ratios from Laan 2010, because these data were skewed. In correspondence, Laan described that participants were unwilling to have blood samples drawn and that data from all endpoints could not be retrieved.

We were unable to use the cognitive test results from the Rey Auditory Verbal Learning Test, the Purdue Pegboard Test, the HQ Continuous Performance Test (Rosvold 1956), and the Trail Making Test (Mezzich 1980) in Laan 2010 because either they were not reported or available in sufficient detail.

Excluded studies

We excluded one study because there was no indication that it was randomised and the measured outcomes were not relevant this review (Rasheed 1992). This study measured blood levels of chlorpromazine and interactions of aspirin in the metabolism of chlorpromazine in people with schizophrenia compared with healthy men. The authors of this study suggested that aspirin might prolong or enhance the therapeutic effects of chlorpromazine by slowing down its metabolism.

Studies awaiting assessment

Weiser 2012 and Weiser 2016 were both randomised, parallel studies comparing antipsychotic medication and adjunct aspirin with antipsychotic medication and adjunct placebo. Weiser 2016 may be a subset of Weiser 2012. We contacted the authors of these studies; Weiser 2016 replied that data from their study were not usable yet.

Ongoing studies

There are four ongoing studies of the higher 1000 mg/day dose of aspirin with 240 participants. Data from these studies would substantially improve the evidence base, especially for specific outcomes such as immunological markers and global state. NCT02047539 kindly replied to our email, saying that this study was still recruiting participants. NCT02685748 kindly replied that 17 participants were enrolled for the study, but no data were available at this time. We have not yet received no replies from IRCT201108197373N1 and IRCT201109287660N1.

Risk of bias in included studies

See the relevant 'Risk of bias' tables in the Characteristics of included studies table; Figure 2; and Figure 3.

Allocation

Both of the included studies stated they were randomised and used computer-generated random sequences to allocate participants and were at low risk of this bias (Attari 2017; Laan 2010). Neither publication reported sufficient information on the method of allocation concealment but, in correspondence, the authors of Laan 2010 kindly provided further details (low risk of bias). Attari 2017 was at unclear risk of bias.

Blinding

Both studies explicitly referred to how participants and assessors were blinded and were at low risk of bias (Attari 2017; Laan 2010).

Incomplete outcome data

There was little evidence of attrition bias (low risk of attrition bias). In Attari 2017, all participants completed the study. In Laan 2010, 12 participants left the study early and used LOCF to impute the missing data.

Selective reporting

The included studies were at high or unclear risk of reporting bias. This was due to either incomplete reporting of expected outcomes (high risk; Laan 2010) or retroactive registration of the protocol (unclear risk; Attari 2017).

Other potential sources of bias

Attari 2017 contained many apparent typographical errors and inconsistencies in the results tables which we have detailed in the Characteristics of included studies table (high risk of other bias). Two review authors (EP and LS) contacted the authors to clarify these inconsistencies but have not yet received a reply. Laan 2010 was at low risk of other bias.

Effects of interventions

See: **Summary of findings for the main comparison** Aspirin plus antipsychotics compared to placebo plus antipsychotics for people with schizophrenia

1. Aspirin plus antipsychotics versus placebo plus antipsychotics

Both included studies randomised participants to receive aspirin or placebo, in addition to their regular antipsychotic medication.

1.1 Global state: any change - unspecified problem necessitating change in dose or type of antipsychotics - medium term

Laan 2010 reported data on the need to change dose or type of antipsychotic. There was no clear difference between treatment groups for this outcome (RR 0.75, 95% CI 0.30 to 1.88; studies = 1; participants = 70; very low-quality evidence; Analysis 1.1).

1.2 Mental state: 1. General - mean endpoint score (PANSS total, high = poor)

Both included studies reported on general mental state using PANSS total endpoint scores (Analysis 1.2; Attari 2017; Laan 2010).

1.2.1 Short term

At short term, there was no clear difference in endpoint scores (MD -1.84, 95% CI -7.55 to 3.87; studies = 2; participants = 130). This subgroup had moderate levels of heterogeneity (Chi^2 = 2.1; degrees of freedom (df) = 1.0; P = 0.15; I^2 = 52%).

1.2.2 Medium term

By eight to 24 weeks, those participants allocated adjunct aspirin had clearly better PANSS total endpoint scores (MD -6.56, 95% CI -12.04 to -1.08; studies = 2; participants = 130; very low-quality evidence).

1.3 Mental state: 2. Specific - negative symptoms - mean endpoint score (PANSS negative, high = poor)

Both included studies reported negative symptoms using PANSS negative (Analysis 1.3; Attari 2017; Laan 2010).

1.3.1 Short term

In the short term, there was no clear difference between the two treatment groups (MD -0.79, 95% CI -2.85 to 1.27; studies = 2; participants = 130).

1.3.2 Medium term

This equivocal result held true for the medium term (MD -1.81, 95% CI -3.64 to 0.01; studies = 2; participants = 130).

1.4 Mental state: 3. Specific - positive symptoms - mean endpoint score (PANSS positive, high = poor)

Both included studies reported on positive symptoms using PANSS positive (Analysis 1.4; Attari 2017; Laan 2010).

1.4.1 Short term

For positive symptom scores, we found no evidence that adjunct aspirin was clearly different in its effects compared with adjunct placebo (MD -0.87, 95% CI -2.62 to 0.89; studies = 2; participants = 130).

1.4.2 Medium term

By eight to 24 weeks, there was a clear difference between adjunct aspirin and adjunct placebo, favouring adjunct aspirin group (MD -3.39, 95% CI -5.08 to -1.70; studies = 2; participants = 130), but heterogeneity was very high (Chi^2 = 5.63; df = 1.0; P = 0.02; I^2 = 82%).

1.5 Leaving the study early: short-term

Both included studies reported numbers of participants leaving the study early (Analysis 1.5; Attari 2017; Laan 2010).

1.5.1 Any reason

When it came to leaving the study early for any reason, there was no evidence of a clear difference between the two treatment groups (RR 1.12, 95% CI 0.40 to 3.14; studies = 2; participants = 130; very low-quality evidence).

1.5.2 Gastrointestinal complaint - mild

There was no clear difference between adjunct aspirin and adjunct placebo for leaving the study early because of mild gastric complaints (RR 7.82, 95% CI 0.42 to 146.05; studies = 1; participants = 70).

1.5.3 Lack of motivation

There was no clear difference between adjunct aspirin and adjunct placebo for leaving the study early due to 'lack of motivation' (RR 0.67, 95% CI 0.17 to 2.60; studies = 1; participants = 70).

1.5.4 Referral to other centre

There was no clear difference between adjunct aspirin and adjunct placebo for referral to other centre (RR 0.37, 95% CI 0.02 to 8.84; studies = 1; participants = 70).

1.6 Adverse events: 1. Gastrointestinal - dyspeptic symptoms (Likert scale for dyspeptic complaints)

Laan 2010 reported incidence of dyspeptic symptoms where participants as well as assessors indicated the seriousness of these symptoms (Analysis 1.6).

1.6.1 Self-assessed - as 'very serious'

There was no clear difference between adjunct aspirin and adjunct placebo for 'very serious' gastrointestinal events (RR 3.35, 95% CI 0.14 to 79.59; studies = 1; participants = 70).

1.6.2 Self-assessed - as 'serious'

There was no clear difference between adjunct aspirin and adjunct placebo for 'serious' gastrointestinal events (RR 0.22, 95% CI 0.01 to 4.49; studies = 1; participants = 70).

1.6.3 Self-assessed - as 'moderate'

There was no clear difference between adjunct aspirin and adjunct placebo for 'moderate' gastrointestinal events (RR 1.03, 95% CI 0.55 to 1.94; studies = 1; participants = 70; very low-quality evidence)

1.6.4 Researcher assessed - needing medical attention because of gastrointestinal complaint

No participant in either of the groups needed medical attention because of a gastrointestinal complaint (risk difference (RD) 0.00 95% CI -0.05 to 0.05; studies = 1; participants = 70).

1.7 Adverse events: 2. Other

Both included studies reported data for 'other' types of adverse events (Analysis 1.7; Attari 2017; Laan 2010).

1.7.1 General - any adverse events - as defined by each study

There was no clear difference between adjunct aspirin and adjunct placebo for non-specific adverse events of any type (RR 0.56, 95% CI 0.11 to 2.86; studies = 2; participants = 130).

1.7.2 Specific - attempted suicide

There was no clear difference between adjunct aspirin and adjunct placebo for this serious event (RR 1.12, 95% CI 0.07 to 17.22; studies = 1; participants = 70).

1.7.3 Specific - suicidal thoughts

There was no clear difference between adjunct aspirin and adjunct placebo for suicidal thoughts (RR 1.12, 95% CI 0.07 to 17.22; studies = 1; participants = 70).

1.7.4 Specific - requiring daily routine restructuring

There was no clear difference between adjunct aspirin and adjunct placebo for this outcome (RR 0.37, 95% CI 0.02 to 8.84; studies = 1; participants = 70).

1.8 Service use: change in hospital status

Laan 2010 reported service use data as 'change in hospital status' (Analysis 1.8).

1.8.1 Admitted to closed ward - because of suicidal thoughts

There was no clear difference between the treatment groups for this outcome (RR 1.12, 95% CI 0.07 to 17.22; studies = 1; participants = 70).

1.8.2 Admitted to open ward - for daily routine restructuring

There was no clear difference between adjunct aspirin and adjunct placebo for this outcome (RR 0.37, 95% CI 0.02 to 8.84; studies = 1; participants = 70).

1.8.3 Any change in hospital status

There was no clear difference between the treatment groups for 'any change in hospital status' (RR 0.56, 95% CI 0.05 to 5.90; studies = 1; participants = 70; very low-quality evidence).

DISCUSSION

Summary of main results

See Summary of findings for the main comparison.

1. Aspirin plus antipsychotics compared to placebo plus antipsychotics for people with schizophrenia

1.1 Global state: any change - unspecified problem necessitating change in dose or type of antipsychotics - medium term

No study reported the prespecified binary global state outcome we had stipulated in our protocol (clinically important change in global state; Roberts 2016). The above outcome is a proxy and we downgraded the quality of evidence rating because of this. We considered whether 'clinically important change in global state' would be unreasonable to expect from trials but continued to feel that such a simple and useful outcome could be expected. Currently there is no indication that additional aspirin helps avoid or increases the need for antipsychotic change (RR 0.75, 95% CI 0.30 to 1.88; studies = 1; participants = 70; very low-quality evidence).

1.2 Mental state: 1. General - mean endpoint score - total (PANSS, high = poor) - medium term

The mental state outcome reported by the trials was a proxy for what we had intended to report (clinically important change in mental state). The fine-grain measure of the PANSS mean endpoint scores reported some suggestion of an improvement in mental state scores for the aspirin group but the meaning of this for day-to-day care was not clear to us and was not explained in the trial (MD -6.56, 95% CI -12.04 to -1.08; studies = 2; participants = 130; very low-quality evidence).

1.3 Leaving the study early: short-term - any reason

Less than 10% of participants in each group left the study early - at around three months - but there was no clear difference between the groups (RR 1.12, 95% CI 0.40 to 3.14; studies = 2; participants = 130; very low-quality evidence). This result suggests people with schizophrenia did not find adding aspirin to antipsychotic treatment unacceptable, but data were very limited quality.

1.4 Adverse events: Gastrointestinal - dyspeptic symptoms - self assessed - 'moderate'

There is an enduring concern with aspirin that it is associated with a risk of gastric problems. These short trials did not highlight a clear difference (RR 1.03, 95% CI 0.55 to 1.94; studies = 1; participants = 70; very low-quality evidence), but data were of very limited quality, and both trials protected their participants from gastric upset by giving pantoprazole or omeprazole.

1.5 Service use: change in hospital status - any change

Reported data suggested adding aspirin to regular antipsychotics did not have a clear effect on 'change in a person's hospital status' (positive or negative was not clear from the report) (RR 0.56, 95% CI 0.05 to 5.90; studies = 1; participants = 70; very low-quality data). However, these data were few and very low quality and, therefore, no conclusion about a difference could be drawn at this point.

1.6 Missing data

1.6.1 Cognitive functioning

At this point, no data related to this important outcome could be included in the analysis. There were data recorded and the authors of Laan 2010 kindly attempted to find usable data but were unable to retrieve them. This is an example of where data for outcomes, thought to be important enough to gather from participants are lost (Chalmers 2009).

1.6.2 Quality of life

At this point, no trial attempted to measure this outcome that is important to service users. Quality of life was less measured in trials of the last century, but now such outcomes are to be expected to be routine and for them not to be included could suggest service user participation in trial design was absent.

Overall completeness and applicability of evidence

1. Completeness

We know randomised trials attempting to test the value of adding aspirin to routine use of antipsychotic treatment have taken place. We also know that there are unpublished data within these original trials that could have added to the evidence. Despite the kind efforts of the Laan 2010 authors, not all of these could be found. Furthermore, we know of fully unpublished trials which have gained informed consent, been undertaken and completed, and not reported at all (Weiser 2012; Weiser 2016). Therefore, the data we presented here are only part of the complete picture already in existence.

Even when we did have numerical data to report, these were from very small studies with limited duration. No outcome we reported was a definitive finding. All outcome data were grossly incomplete should clinicians, researchers or recipients of care feel the addition of aspirin to medication be an important question. If this story is to be completed, then much larger, longer, clinically meaningful

trials should be undertaken, which should be clearly reported and disseminated.

2. Applicability

The two small studies included in this review included people with schizophrenia who had been diagnosed using DSM-IV criteria. This could indicate that the population of these trials is made up of patients who might be rare in every day clinical practice as many people coming to clinic may not fall within the rigorous definition of the DSM. One study was carried out in Iran and the other in the Netherlands.

Aspirin is a globally available, low-cost drug and, therefore, an accessible intervention.

Quality of the evidence

Overall the quality of the evidence was not good. Only two studies with 130 participants could be included in the review. One of the included studies had multiple inconsistencies in reporting values (Attari 2017), and Laan 2010 demonstrated some evidence of selective reporting. Attari 2017 reported that there were no adverse events due to either aspirin or antipsychotics and did not publish their protocol before the study. It seems unlikely, although not impossible, that over a span of 10 weeks not one of the 60 participants experienced an adverse event.

Poor reporting of several outcomes, including immunological parameters and cognitive outcomes, made the data impossible to use within a meta-analysis. Neither study addressed several of the outcomes review authors considered important and prespecified as such in the protocol (Roberts 2016), including people's quality of life and the economic value of the intervention.

Potential biases in the review process

1. Missing studies

Every effort was made to identify relevant studies. It is possible that we missed small, relevant studies but it seems unlikely that we have missed any large studies that would have substantially altered the conclusions of the review.

2. Introducing bias

We tried to be balanced in our appraisal of the evidence but could have inadvertently introduced bias. Given the small number of included studies, two review authors independently inspected all citations obtained from the search and extracted the data to minimise bias. We welcome comments or criticisms.

Agreements and disagreements with other studies or reviews

Sommer 2012 conducted a meta-analysis on non-steroidal anti-inflammatory drugs for schizophrenia, including Laan 2010 and four small studies on celecoxib. They focused on PANSS total and subscale scores. This analysis showed very small positive effects for non-steroidal anti-inflammatory drug; however, the few included studies were small and potential publication bias was discussed.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with schizophrenia

Theoretically aspirin may reduce inflammation associated with schizophrenia and therefore reduce symptoms. However, studies to date have provided insufficient evidence that aspirin actually improves the symptoms or lives of people with schizophrenia. Limited data show aspirin has a very narrow positive effect in the medium term (eight weeks to six months) on the total PANSS scale. However, at doses of 500 mg or 1000 mg, aspirin appears to cause no more or no fewer significant adverse effects when compared to placebo, but this is based on very few data. Therefore, while aspirin is unlikely to effectively treat the symptoms of schizophrenia, there are insufficient data to make final conclusions about potential, long-term, adverse effects.

The publication of several studies that are currently either ongoing or awaiting publication, with many more participants, would improve the evidence base substantially. There are no usable data available on whether aspirin affects aspects of cognitive functioning, service utilisation or levels of inflammation markers of people with schizophrenia. In addition, no study attempted to measure the impact of aspirin on people's quality of life or its economic value, which is relevant as aspirin is more affordable than most novel treatments for schizophrenia. Therefore, in the context of a randomised controlled trial, the intervention would be feasible.

2. For clinicians

The results of this review suggest that aspirin may improve the mental state of people with schizophrenia in the medium term; however, the small amount of data included in this analysis may lead to an overestimation of the effects of aspirin.

Data on gastrointestinal complaints are very limited and therefore, no clear advice can be given on this very important topic. Additionally, both trials gave gastric protection to participants and none of the presently available studies provide data on long-term effects. Therefore, it is unclear whether the benefits of prescribing

aspirin over a longer period outside of the scope of a trial would outweigh the possible risks and could raise ethical concerns.

3. For policy makers

For policy making, the limited available evidence does not suggest a need for integrating adjunct aspirin as a mainstream intervention for schizophrenia. No data on hospitalisation or functioning are available and data on service use are very limited.

Implications for research

1. General

In order to prevent publication bias, protocols should be registered prior to publication. In the context of this, and other interventions, transparency and clear reporting of both methodology and results makes it easier to assess validity of the results and facilitates the reviewing process.

Binary data are usually easier to interpret and for all outcomes that necessitate continuous outcomes, providing some measures of variance is helpful.

To reduce uncertainty and expenditure of time, data presented in graphs should be accompanied by tables or text references with exact numbers and standard deviations (SD), for this review preferably as endpoint, and not as change scores. To enhance transparency, and to gain access to the statistical values needed for this review, Laan 2010 provided individual patient data from the trial. This was very helpful to us, and systematic reviews could profit from this practise in general.

2. Specific

2.1 Reviews

The protocol for a review on the effects of celecoxib was published in the Cochrane Library (Akhondzadeh 2011). Celecoxib is another potential NSAID intervention for schizophrenia that might have an anti-inflammatory effect and therefore, the review for this protocol should proceed. Additionally, aspirin and celecoxib data might be investigated in the same context.

2.2 Trials

At the point of writing this review (July 2018) we know of several important relevant studies. Weiser 2012 is completed and is thought to involve around 200 participants relevant to this review. The four other ongoing studies may also add hundreds of people's data to the comparisons within this review (IRCT201108197373N1; IRCT201109287660N1; NCT02047539; NCT02685748). It is possible, that, within a few years, the appended data will strengthen the evidence base to a point where no more trials are needed. We eagerly await the reports of the new trials.

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Structuring of the text about used outcomes in the 'Characteristics of included studies' table was supported by the "OutcomesApp". More information is available at github.com/CochraneSchizophrenia/OutcomesApp/releases

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Attari 2017

Methods	Allocation: randomised, stratified by baseline PANSS scores Blinding: triple Design: parallel Duration: 10 weeks
Participants	Diagnosis: schizophrenia (DSM-IV-TR, clinical interview) n = 60 Age: mean 33 years, SD 8 Gender: 39 men, 21 women History: 2 years since onset of the disease. Patients with acute symptoms referred to psychiatric clinic or emergency department Inclusion criteria: aged 18-65 years, 2 years since onset Exclusion criteria: unwillingness to participate; failure to follow-up for whatever reason; unstable medical illness and medical history; contraindications for use of aspirin: asthma or seasonal allergies, ulcers, kidney disease, active bleeding or clotting of blood disorders such as haemophilia or bleeding, gout, nasal polyps, chronic use of NSAID, concomitant use of corticosteroids for any reason; maternity Setting: psychiatric clinic, single centre Country: Iran
Interventions	1. Aspirin 325 mg/day + regular antipsychotics[a], omeprazole 20 mg/day. n = 20[b] 2. Aspirin 500 mg/day + regular antipsychotics[a], omeprazole 20 mg/day. n = 20 3. Placebo oral tablet daily + regular antipsychotics, omeprazole 20 mg/day. n = 20
Outcomes	Mental state: PANSS total, negative, positive[c] Adverse events: any Leaving the study early: any reason Unable to use: Mental state: PANSS general psychopathology (not validated subscore)
Notes	[a] Chlorpromazine, risperidone, olanzapine, haloperidol [b]Group receiving aspirin 325 mg is assumed to have a typo in Table 1: it says 20 male participants, while all other numbers (total, percentages in gender distribution) point to only 12 male participants. We assumed 12 participants for this group throughout this review [c]PANSS subscale scores did not always add up to the printed total in the tables. We contacted authors for clarification but at the time of writing this report have not received a reply

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Quote: "The patients, through a number table, were randomly divided", "stratified randomization was used", "the randomization sequence was computer-generated, with the randomization itself conducted through SPSS20 software", "Randomization was done by one of the researchers, who did not have a role in the treatment" Comment: Table 2 indicated that baseline PANSS scores differed significantly between the control and treatment groups. However, the SDs of the groups overlapped
Allocation concealment (selection bias)	Unclear risk	Quote: "Allocation concealment was done by the researcher, who was responsible for the randomization. For this purpose, the numbered envelops that contained the name of the drugs … were used", "participants were referred to the hospital's pharmacy to obtain their drugs", "A resident of psychiatry generated the random allocation sequence and enrolled participants, and a co-worker psychologist assigned participants to their interventions" Comment: unclear if opaque, sealed envelopes used.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "placebo tablets had the same shape and color of the effective aspirin", "Drug and placebo were coded A, B and C", "Neither the examiner nor the clinician and the patient were aware of the drug compounds" Comment: see Materials and methods section.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The PANSS scale was administered on the first day, the end of the sixth week and one month after cessation of aspirin or placebo", "The outcomes of the study were recorded by the psychiatrist of the psychiatry ward, who made no other contribution to the study" Comment: no indications that adverse effects led to detection of allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to follow-up.

Attari 2017 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Outcomes reported as stated in protocol, but retrospective registration of protocol
Other bias	High risk	Reporting bias: inconsistent reporting of values between number tables, minor mistakes with numbers not adding up correctly (see 'Notes' in Characteristics of included studies table). Authors were contacted to clarify the typographical errors, however, there was no response No adverse events recorded for aspirin or antipsychotics, which is not impossible, but unlikely

Laan 2010

Methods	Allocation: randomised, stratified by psychiatric centre and immunological parameters Blinding: double Design: parallel Duration: 3 months, preceded by 2 weeks placebo run-in
Participants	Diagnosis: schizophrenia spectrum disorder (DSM-IV) n = 70 Age: mean 31 years, SD 9 years Gender: 58 men, 12 women History: people taking antipsychotics Inclusion criteria: PANSS score ≥ 60 (a minimum of 2 items had to have a score of ≥ 4), aged 18-55 years Exclusion criteria: illness duration > 5 years initially - lengthened to 10 years due to slow enrolment, contraindications for aspirin or pantoprazole, significant somatic illness, chronic NSAID use, corticosteroid use, pregnancy, change of type or dose of antipsychotic in last 2 weeks Setting: inpatients and outpatients, multicentre Country: Netherlands
Interventions	1. Aspirin 1000 mg/day (oral) + regular antipsychotics[b], pantoprazole 40 mg/day. n = 33 2. Placebo daily (oral tablet) + regular antipsychotics, pantoprazole 40 mg/day. n = 37
Outcomes	Global state: necessitating change in dose or type of antipsychotics Mental state: PANSS total, negative, positive Adverse events: gastrointestinal, any adverse events, attempted suicide, suicidal thoughts, requiring daily routine restructuring Leaving the study early: any reason, specific reasons Service utilisation: change in hospital status (admitted to closed ward - because of suicidal thoughts, admitted to open ward - for daily routine restructuring, any change) Unable to use: Mental state: PANSS general psychopathology (not validated subscore)

Laan 2010 (*Continued*)

	Cognitive functioning: changes in Rey Auditory Verbal Learning Test, Purdue Pegboard Test, HQ Continuous Performance Test, Trail Making Test scores (not adequate outcome data) Inflammatory markers: T_H1/T_H2 cytokine ratios (only reported for baseline, missing data from follow-up).[a]
Notes	[a]Authors were contacted to retrieve missing immunological and cognitive data. The author kindly responded but these data could not be retrieved [b] Olanzapine, clozapine and risperidone were described as the antipsychotics used by most of the participants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients will be randomised in a 1:1 ratio to either supplementation of acetylsalicylic acid or placebo in addition to their current antipsychotic treatment"; "a computer generated list will be produced with allocation codes in random order … using permuted blocks"
Allocation concealment (selection bias)	Low risk	No information provided in publication. The main author was contacted and kindly replied that randomisation was done in the university pharmacy, medications were labelled with randomly generated numbers, and the link between the medication number and treatment group was kept in a safe
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Placebo will be identically packaged, looking and tasting tablets"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All outcome assessments were performed blind to the randomised treatment status" Comment: no evidence that blinding was tested. The main author provided extra information that statistical analysis was performed blind to the treatment status of each cluster
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Twelve patients (17%), six in each group, did not complete follow-up" Comment: reasons for loss to follow-up were well recorded. More participants in the experimental arm left due to mild gas-

Laan 2010 (*Continued*)

		trointestinal adverse effects than in the placebo arm. Used last observation carried forward
Selective reporting (reporting bias)	High risk	T_H1/T_H2 cytokine ratios, a secondary outcome specified in the protocol, were reported at baseline for each group but not for follow-up Comment: contacted main author but data could not be recovered
Other bias	Low risk	No other biases evident.

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision; n: number of participants; NSAID: non-steroidal anti-inflammatory drug; PANSS: Positive and Negative Symptom Scale; SD: standard deviation.

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

Study	Reason for exclusion
Rasheed 1992	Allocation: not randomised Participants: people with schizophrenia were compared with healthy individuals, all men Outcomes: not of interest to this review: serum chlorpromazine concentration; serum salicylate concentration; urinary excretion of drugs

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

Weiser 2012

Methods	Allocation: randomised Blinding: not reported Design: parallel Duration: 16 weeks
Participants	Diagnosis: schizophrenia or schizoaffective disorder n = 400 Age: mean 42 years Gender: 50% women History: mean illness duration 13 years Inclusion criteria: ≥ 4 (moderate) on CGI-S, ≥ 4 (moderate) on PANSS items (delusions, hallucinatory behaviours, conceptual disorganisation or suspiciousness/persecution), total PANSS negative score > 18 Setting: multicentre

Weiser 2012 (*Continued*)

Interventions	1. Aspirin 1000 mg/day (oral) + antipsychotics + pantoprazole 40 mg/day 2. Minocycline 200 mg/day (oral) + antipsychotics 3. Pramipexole 1.5 mg/day (oral) + antipsychotics 4. Placebo daily (oral) + antipsychotics
Outcomes	Mental state: change in PANSS score (total and subscales: positive symptoms, negative symptoms) Global state: change in CGI
Notes	Awaiting useable data

Weiser 2016

Methods	Allocation: randomised Blinding: not reported Design: parallel Duration: 16 weeks
Participants	Diagnosis: schizophrenia or schizoaffective disorder n = 160 Age: mean about 41.5 years History: mean duration of illness 9 years; mean baseline PANSS 101 Inclusion criteria: see Weiser 2012 inclusion criteria; high plasma CRP levels (> 3850 ng/mL)
Interventions	1. Aspirin 1000 mg/day + antipsychotics. n = 80 2. Placebo daily + antipsychotics. n = 80
Outcomes	Mental state: change in PANSS score (total and subscales: positive symptoms, negative symptoms) Cognitive functioning: "cognition"
Notes	Probably a subset of Weiser 2012 participants who had high plasma CRP levels. Awaiting useable data

CGI-S: Clinical Global Impression - Severity scale; CRP: C-reactive protein; n: number of participants; PANSS: Positive and Negative Symptom Scale.

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

IRCT201108197373N1

Trial name or title	Efficacy of aspirin in treatment of schizophrenia
Methods	Allocation: randomised Blinding: triple Duration: 8 weeks

IRCT201108197373N1 (*Continued*)

Participants	Diagnosis: schizophrenia according to DSM-IV criteria and clinical interview by psychiatrist n = 60 Age: range 15-55 years Gender: both Inclusion criteria: PANSS score > 60 Exclusion criteria: pregnancy; substance abuse; sever physical disease such as kidney disease; coagulation disorders; gastrointestinal disorders such as peptic ulcer; contraindications of aspirin and inhibitors of proton pump Country: Iran
Interventions	1. Aspirin 1000 mg/day + atypical antipsychotic 2. Placebo daily + atypical antipsychotic
Outcomes	Mental state: PANSS Adverse events: extrapyramidal and gastrointestinal adverse effects
Starting date	Recruitment start date: 23 October 2011
Contact information	Dr Hamidreza Jamilian, jamilian.hr@arakmu.ac.ir
Notes	Protocol and outcome data not available. Attempted to contact author

IRCT201109287660N1

Trial name or title	Effect of aspirin augmentation on cognitive and clinical symptoms of schizophrenic patients
Methods	Allocation: randomised Blinding: double Duration: 12 weeks
Participants	Diagnosis: schizophrenia according to DSM-IV criteria n = 40 History: admitted to Ibn Sina hospital of Mashhad Inclusion criteria: PANSS score > 60; duration of illness < 5 years and 1-3 episodes Exclusion criteria: physical disease based on clinical examination; chronic use of NSAIDs; corticosteroid use; pregnancy, contraindication for aspirin or omeprazole; other drug use (except for anticholinergics and benzodiazepines) Country: Iran
Interventions	1. Aspirin 1000 mg/day + risperidone dose started at 2 mg and increased to 6 mg or maximum dose tolerated by patient 2. Placebo daily + risperidone dose same as group 1
Outcomes	Mental state: PANSS Cognitive functioning: Weschler, Wisconsin, Stroop, BPRS, Digit Span tests
Starting date	Recruitment start date: 21 December 2013

IRCT201109287660N1 (*Continued*)

Contact information	ramresearch@mums.ac.ir
Notes	Attempted to contact author to enquire about outcomes

NCT02047539

Trial name or title	Randomized controlled trial of aspirin vs placebo in the treatment of patients with the clinical risk syndrome for psychosis
Methods	Allocation: randomised Blinding: double Duration: 12 weeks
Participants	n = 40 Age: 19-35 years Gender: both Inclusion criteria: demonstrate adequate decisional capacity; meet ≥ 3 of the clinical high-risk symptoms defined by Structured Interview for Prodromal Symptoms Exclusion criteria: pre-existing gastrointestinal disease; heart disease; kidney disease; use of NSAIDs; hypersensitive to NSAID; coexisting unstable major medical illness; pregnant or breastfeeding; consume > 2 drinks of alcohol per day; have a blood clotting disorder; taking angiotensin-converting enzyme inhibitors; acetazolamide; anticoagulants; anticonvulsants; beta-blockers; diuretics; methotrexate; oral hypoglycaemic; uricosuric agents; history of substance abuse in the past 3 months or dependence in past 6 months Country: USA
Interventions	1. Aspirin 1000 mg/day 2. Placebo 1000 mg/day
Outcomes	Inflammation markers: laboratory studies of inflammation markers and genetic samples Not used: mental state: Scale of Prodromal Symptoms (written by 1 of the trialists)
Starting date	March 2014
Contact information	Dr Scott W Woods; scott.woods@yale.edu
Notes	Contacted author and the study is still registering participants Funding: Yale University

NCT02685748

Trial name or title	Aspirin in young psychotic patients
Methods	Allocation: randomised Blinding: double Duration: 6 weeks

NCT02685748 (*Continued*)

Participants	Diagnosis: F 20 to F 29 according to ICD-10 criteria n = 100 Age: 18-28 years Gender: both Inclusion criteria: duration of illness < 7 years Exclusion criteria: substance abuse; primary cognitive impairment; contraindications and special caution for aspirin and pantoprazole: hypersensitivity to aspirin and other NSAIDs or panto ulcers, gastritis, pregnancy, haemophilia, bleeding disorders, gout, asthma, COPD, bronchospasm induced by NSAIDs, angio-oedema, haemolytic anaemia, use of warfarin or methotrexate, diabetes, reduced function of liver or kidney (or both) , heart failure, surgical/dental intervention, interactions with certain psychotropic drugs
Interventions	1. Aspirin 1000 mg/day (oral) + pantoprazole 40 mg/day (oral) 2. Placebo daily (oral)
Outcomes	Cognitive functioning: change in Heidelberg Neurological Soft Signs scale; MoCA score Mental state: change in PANSS total score and subscores Inflammation markers: change in C-reactive proteins, white blood cell count, cytokine profile including Th1, Th2, and Type-17 immune response
Starting date	March 2016
Contact information	Dr Dragana Pavicevic, gagapavicevic@yahoo.com
Notes	Attempted to contact author to enquire about outcomes Funding: Stanley Medical Institute

BPRS: Brief Psychiatric Rating Scale; COPD: chronic obstructive pulmonary disease; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; ICD-10: International Classification of Diseases 10th Revision; MoCA: Montreal Cognitive Assessment scale; n: number of participants; NSAID: non-steroidal anti-inflammatory drug; PANSS: Positive and Negative Syndrome Scale.

DATA AND ANALYSES

Comparison 1. Aspirin plus antipsychotics versus placebo plus antipsychotics)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global state: any change - unspecified problem necessitating change in dose or type of antipsychotics - medium term	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.30, 1.88]
2 Mental state: 1. General - mean endpoint score (Positive and Negative Symptom Scale (PANSS) total, high = poor)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Short term	2	130	Mean Difference (IV, Fixed, 95% CI)	-1.84 [-7.55, 3.87]
2.2 Medium term	2	130	Mean Difference (IV, Fixed, 95% CI)	-6.56 [-12.04, -1.08]
3 Mental state: 2. Specific - negative symptoms - mean endpoint score (PANSS negative, high = poor)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Short term	2	130	Mean Difference (IV, Fixed, 95% CI)	-0.79 [-2.85, 1.27]
3.2 Medium term	2	130	Mean Difference (IV, Fixed, 95% CI)	-1.81 [-3.64, 0.01]
4 Mental state: 3. Specific - positive symptoms - mean endpoint score (PANSS positive, high = poor)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Short term	2	130	Mean Difference (IV, Fixed, 95% CI)	-0.87 [-2.62, 0.89]
4.2 Medium term	2	130	Mean Difference (IV, Fixed, 95% CI)	-3.39 [-5.08, -1.70]
5 Leaving the study early: short-term	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Any reason	2	130	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.40, 3.14]
5.2 Due to gastrointestinal complaint - mild	1	70	Risk Ratio (M-H, Fixed, 95% CI)	7.82 [0.42, 146.05]
5.3 Lack of motivation	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.17, 2.60]
5.4 Referral to other centre	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.02, 8.84]
6 Adverse events: 1. Gastrointestinal - dyspeptic symptoms (Likert scale for dyspeptic complaints)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Self-assessed - as 'very serious'	1	70	Risk Ratio (M-H, Fixed, 95% CI)	3.35 [0.14, 79.59]
6.2 Self-assessed - as 'serious'	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.01, 4.49]
6.3 Self-assessed - as 'moderate'	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.55, 1.94]
6.4 Researcher assessed - needing medical attention because of gastrointestinal complaint	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

7 Adverse events: 2. Other	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 General - any adverse events - as defined by each study	2	130	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.11, 2.86]
7.2 Specific - attempted suicide	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.07, 17.22]
7.3 Specific - suicidal thoughts	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.07, 17.22]
7.4 Specific - requiring daily routine restructuring	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.02, 8.84]
8 Service use: change in hospital status	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Admitted to closed ward - because of suicidal thoughts	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.07, 17.22]
8.2 Admitted to open ward - for daily routine restructuring	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.02, 8.84]
8.3 Any change in hospital status	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.05, 5.90]

Analysis 1.1. Comparison 1 Aspirin plus antipsychotics versus placebo plus antipsychotics), Outcome 1 Global state: any change - unspecified problem necessitating change in dose or type of antipsychotics - medium term.

Review: Acetylsalicylic acid (aspirin) for schizophrenia

Comparison: 1 Aspirin plus antipsychotics versus placebo plus antipsychotics)

Outcome: 1 Global state: any change – unspecified problem necessitating change in dose or type of antipsychotics – medium term

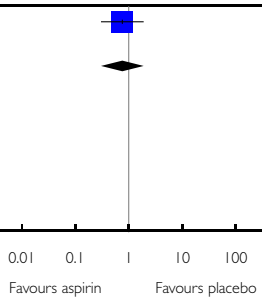
Study or subgroup	Aspirin + antipsychotics n/N	Placebo + antipsychotics n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Laan 2010	6/33	9/37		100.0 %	0.75 [0.30, 1.88]
Total (95% CI)	**33**	**37**		**100.0 %**	**0.75 [0.30, 1.88]**

Total events: 6 (Aspirin + antipsychotics), 9 (Placebo + antipsychotics)

Heterogeneity: not applicable

Test for overall effect: Z = 0.62 (P = 0.54)

Test for subgroup differences: Not applicable

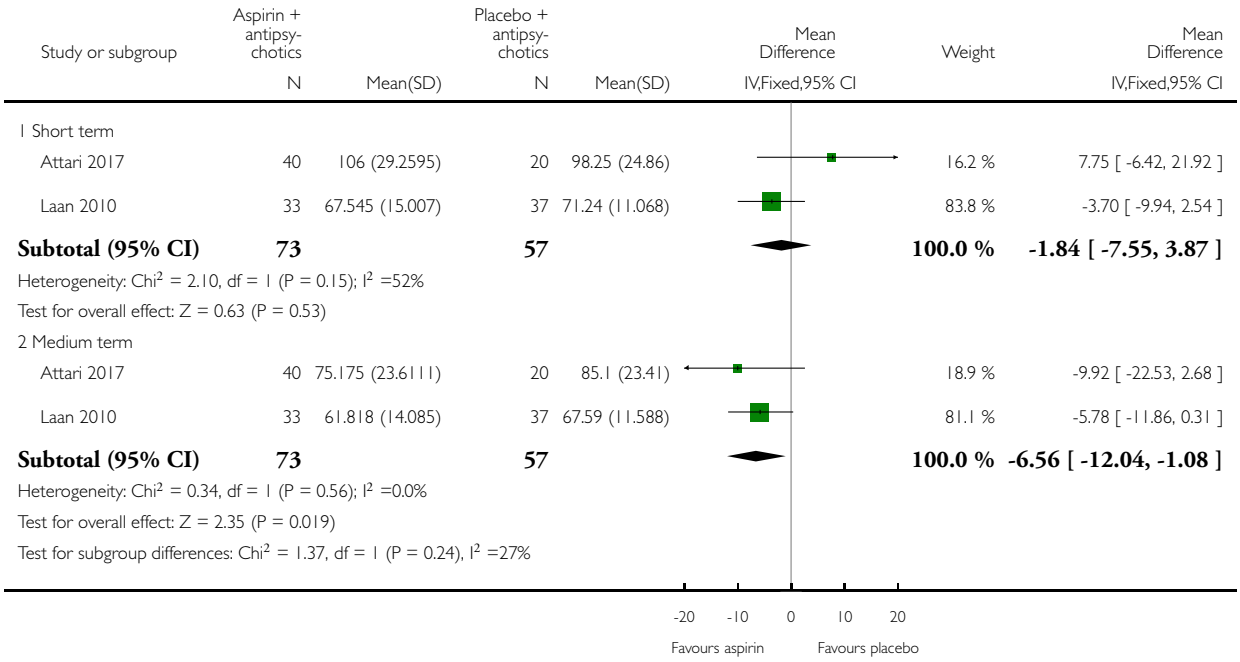


Analysis 1.2. Comparison 1 Aspirin plus antipsychotics versus placebo plus antipsychotics), Outcome 2 Mental state: 1. General - mean endpoint score (Positive and Negative Symptom Scale (PANSS) total, high = poor).

Review: Acetylsalicylic acid (aspirin) for schizophrenia

Comparison: 1 Aspirin plus antipsychotics versus placebo plus antipsychotics)

Outcome: 2 Mental state: 1. General – mean endpoint score (Positive and Negative Symptom Scale (PANSS) total, high = poor)



Analysis 1.3. Comparison 1 Aspirin plus antipsychotics versus placebo plus antipsychotics), Outcome 3 Mental state: 2. Specific - negative symptoms - mean endpoint score (PANSS negative, high = poor).

Review: Acetylsalicylic acid (aspirin) for schizophrenia

Comparison: 1 Aspirin plus antipsychotics versus placebo plus antipsychotics)

Outcome: 3 Mental state: 2. Specific – negative symptoms – mean endpoint score (PANSS negative, high = poor)

Study or subgroup	Aspirin + antipsychotics N	Mean(SD)	Placebo + antipsychotics N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Short term							
Attari 2017	40	27.275 (7.9734)	20	25.7 (9.95)		16.9 %	1.57 [-3.44, 6.59]
Laan 2010	33	17.242 (4.697)	37	18.51 (4.963)		83.1 %	-1.27 [-3.53, 0.99]
Subtotal (95% CI)	**73**		**57**			**100.0 %**	**-0.79 [-2.85, 1.27]**
Heterogeneity: Chi^2 = 1.03, df = 1 (P = 0.31); I^2 =3%							
Test for overall effect: Z = 0.75 (P = 0.45)							
2 Medium term							
Attari 2017	40	18.3 (6.4358)	20	21.8 (8.87)		17.4 %	-3.50 [-7.87, 0.87]
Laan 2010	33	15.788 (4.234)	37	17.24 (4.327)		82.6 %	-1.45 [-3.46, 0.55]
Subtotal (95% CI)	**73**		**57**			**100.0 %**	**-1.81 [-3.64, 0.01]**
Heterogeneity: Chi^2 = 0.69, df = 1 (P = 0.40); I^2 =0.0%							
Test for overall effect: Z = 1.95 (P = 0.052)							
Test for subgroup differences: Chi^2 = 0.53, df = 1 (P = 0.47), I^2 =0.0%							

Analysis 1.4. Comparison 1 Aspirin plus antipsychotics versus placebo plus antipsychotics), Outcome 4 Mental state: 3. Specific - positive symptoms - mean endpoint score (PANSS positive, high = poor).

Review: Acetylsalicylic acid (aspirin) for schizophrenia

Comparison: 1 Aspirin plus antipsychotics versus placebo plus antipsychotics)

Outcome: 4 Mental state: 3. Specific – positive symptoms – mean endpoint score (PANSS positive, high = poor)

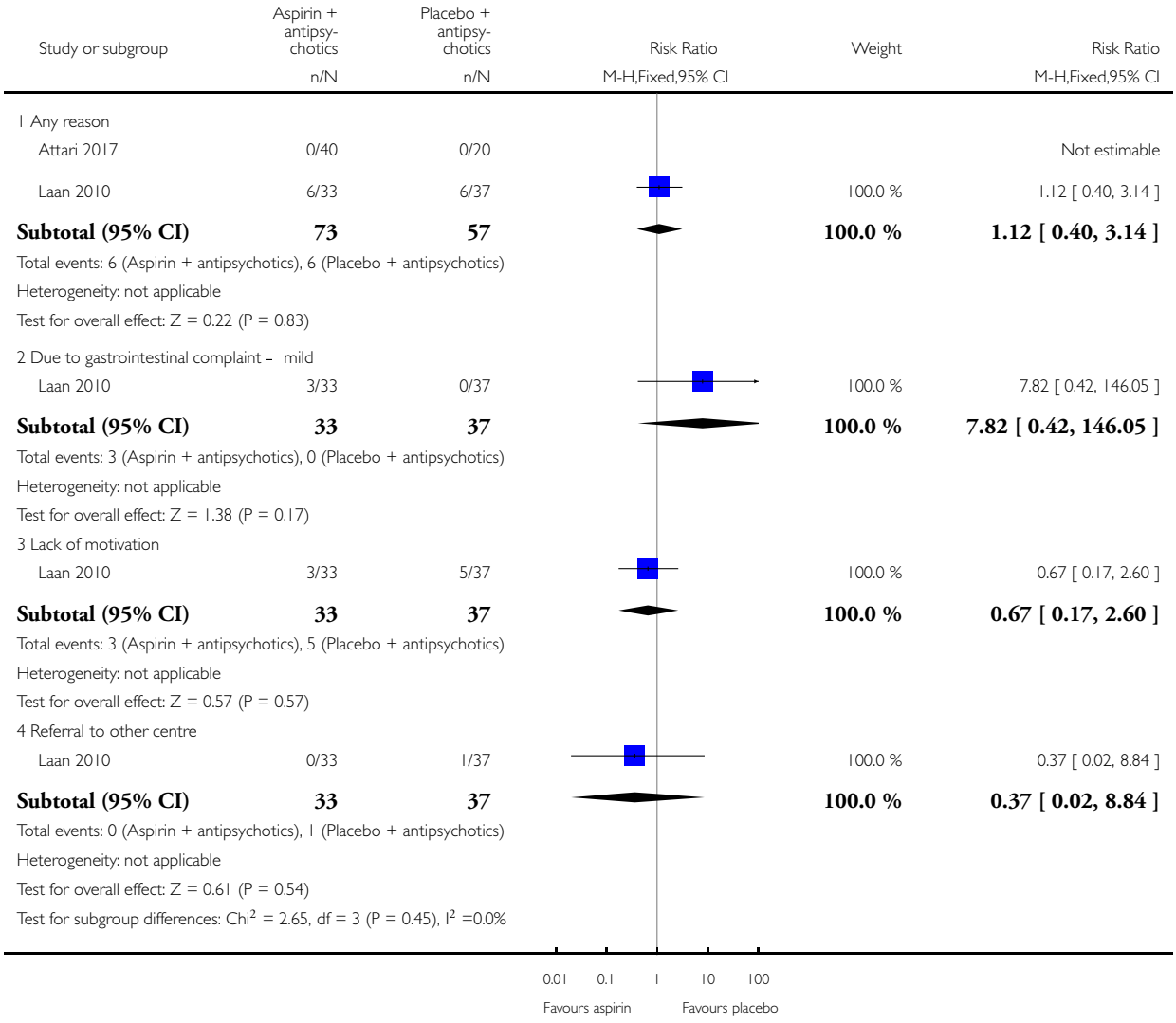
Study or subgroup	Aspirin + antipsychotics N	Mean(SD)	Placebo + antipsychotics N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Short term							
Attari 2017	40	23.75 (5.7628)	20	25.1 (6.74)		26.0 %	-1.35 [-4.80, 2.10]
Laan 2010	33	16.061 (4.905)	37	16.76 (3.642)		74.0 %	-0.70 [-2.74, 1.35]
Subtotal (95% CI)	**73**		**57**			**100.0 %**	**-0.87 [-2.62, 0.89]**
Heterogeneity: Chi^2 = 0.10, df = 1 (P = 0.75); I^2 =0.0%							
Test for overall effect: Z = 0.96 (P = 0.33)							
2 Medium term							
Attari 2017	40	15.125 (4.7494)	20	21.8 (6.48)		28.0 %	-6.68 [-9.87, -3.48]
Laan 2010	33	14.212 (4.504)	37	16.32 (3.953)		72.0 %	-2.11 [-4.11, -0.12]
Subtotal (95% CI)	**73**		**57**			**100.0 %**	**-3.39 [-5.08, -1.70]**
Heterogeneity: Chi^2 = 5.63, df = 1 (P = 0.02); I^2 =82%							
Test for overall effect: Z = 3.92 (P = 0.000087)							
Test for subgroup differences: Chi^2 = 4.11, df = 1 (P = 0.04), I^2 =76%							

Analysis 1.5. Comparison 1 Aspirin plus antipsychotics versus placebo plus antipsychotics), Outcome 5 Leaving the study early: short-term.

Review: Acetylsalicylic acid (aspirin) for schizophrenia

Comparison: 1 Aspirin plus antipsychotics versus placebo plus antipsychotics)

Outcome: 5 Leaving the study early: short-term

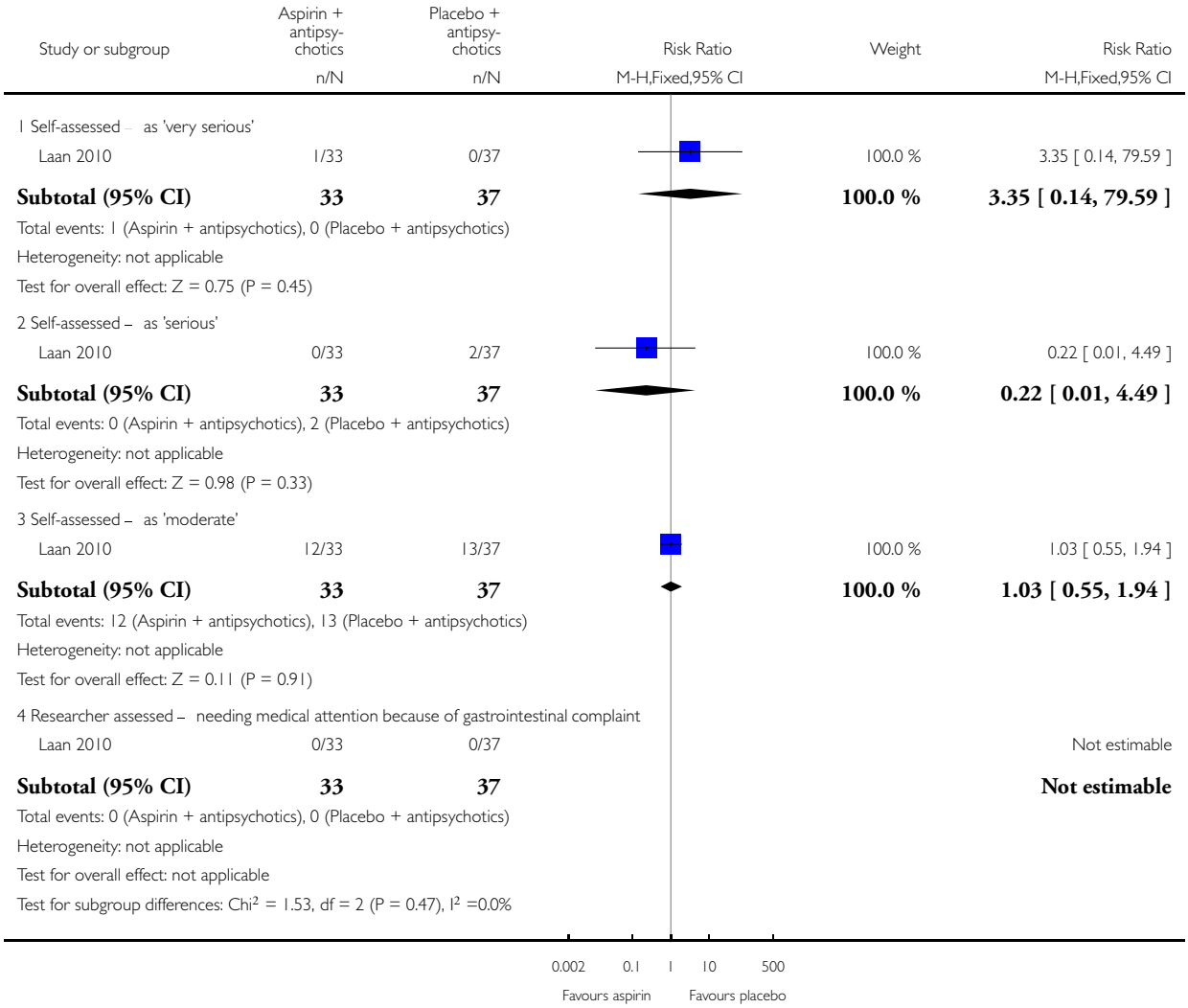


Analysis 1.6. Comparison 1 Aspirin plus antipsychotics versus placebo plus antipsychotics), Outcome 6 Adverse events: 1. Gastrointestinal - dyspeptic symptoms (Likert scale for dyspeptic complaints).

Review: Acetylsalicylic acid (aspirin) for schizophrenia

Comparison: 1 Aspirin plus antipsychotics versus placebo plus antipsychotics)

Outcome: 6 Adverse events: 1. Gastrointestinal – dyspeptic symptoms (Likert scale for dyspeptic complaints)

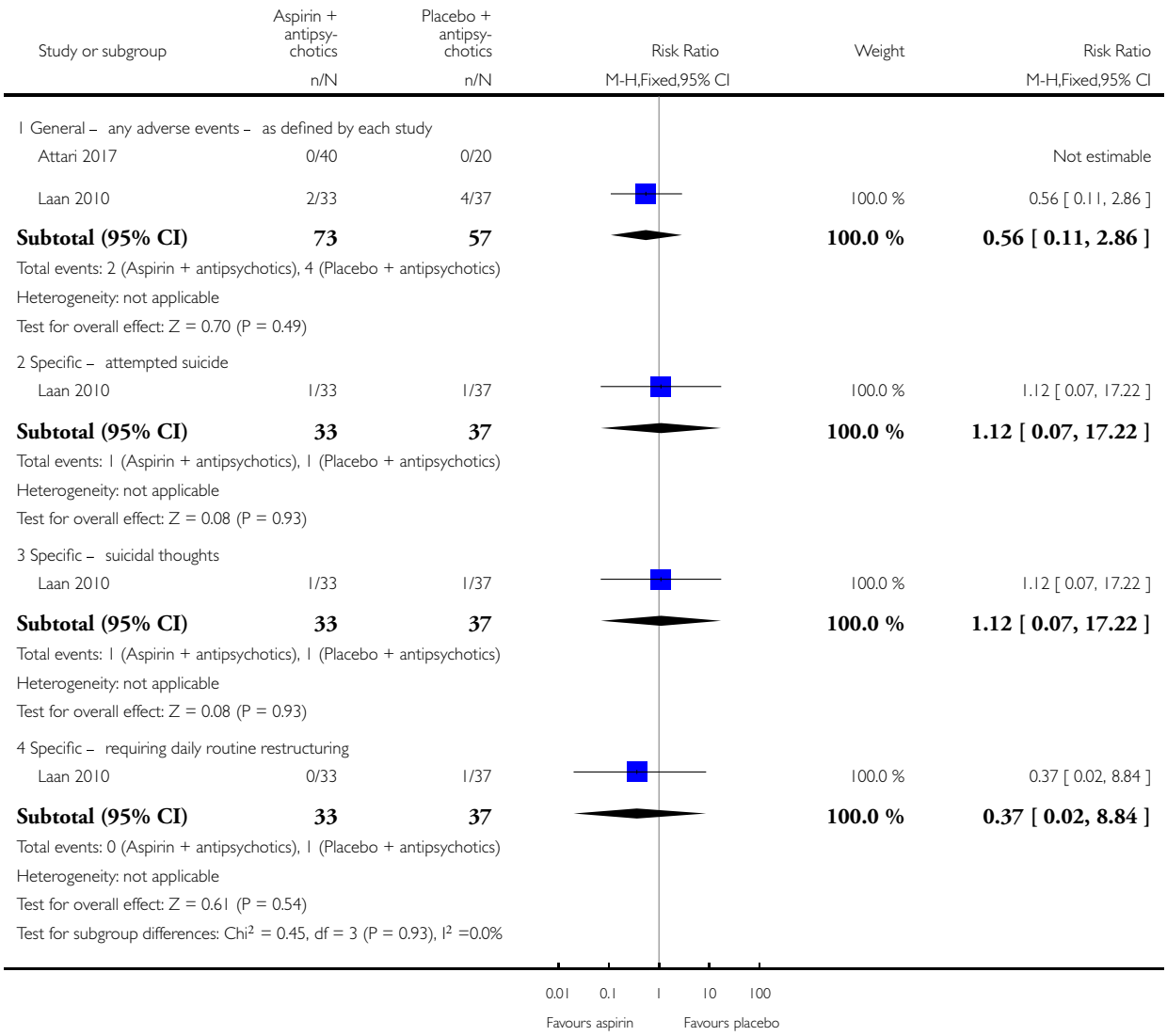


Analysis 1.7. Comparison 1 Aspirin plus antipsychotics versus placebo plus antipsychotics), Outcome 7 Adverse events: 2. Other.

Review: Acetylsalicylic acid (aspirin) for schizophrenia

Comparison: 1 Aspirin plus antipsychotics versus placebo plus antipsychotics)

Outcome: 7 Adverse events: 2. Other

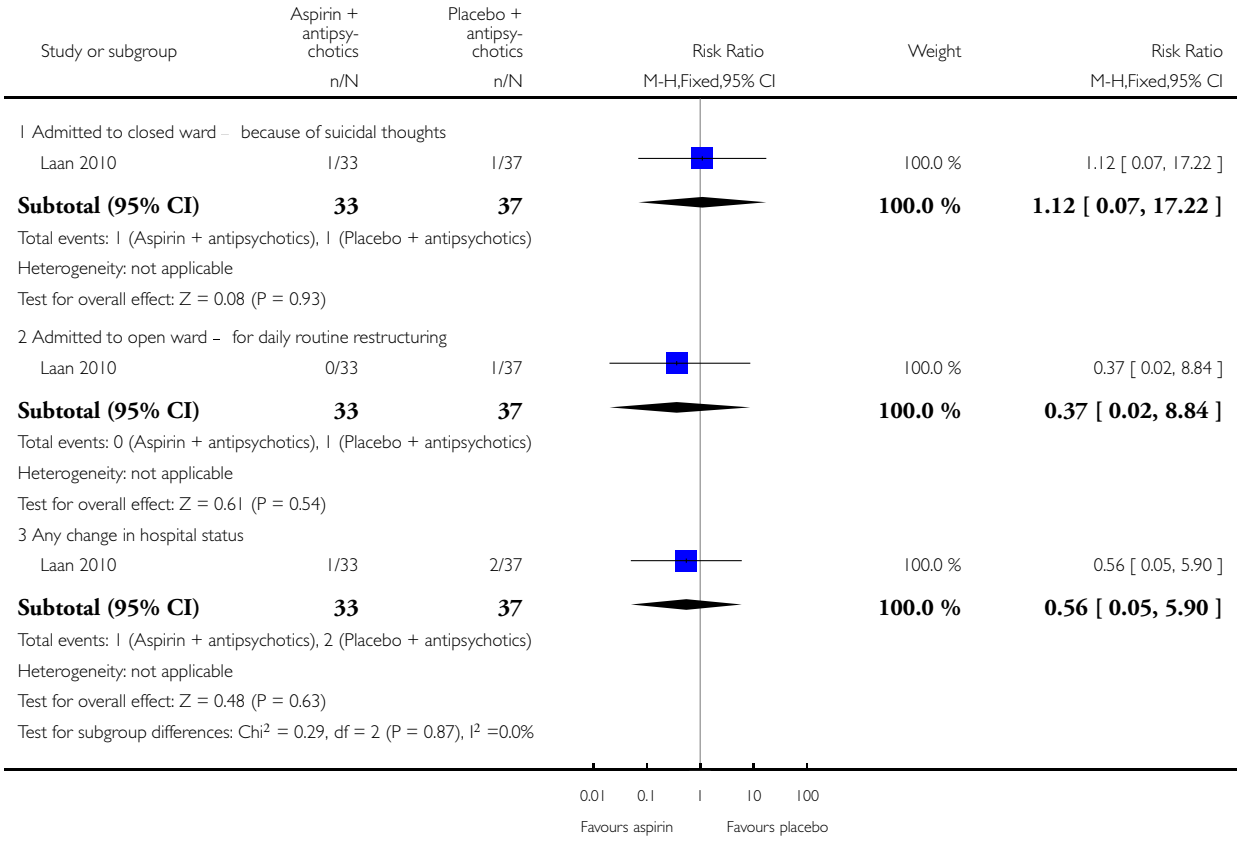


Analysis 1.8. Comparison 1 Aspirin plus antipsychotics versus placebo plus antipsychotics), Outcome 8 Service use: change in hospital status.

Review: Acetylsalicylic acid (aspirin) for schizophrenia

Comparison: 1 Aspirin plus antipsychotics versus placebo plus antipsychotics)

Outcome: 8 Service use: change in hospital status



HISTORY

Protocol first published: Issue 3, 2016

Review first published: Issue 8, 2019

Date	Event	Description
8 March 2018	Amended	Search was updated and 1 new study was added to Ongoing studies section
29 June 2017	Amended	Search updated and 3 references were added to Studies Awaiting Classification section of the review. Please consider that one of the references reports two studies that's why I have added it twice under two different study names. one of the references reports a new study
24 March 2016	Amended	Search updated and 6 studies (16 references) were added to 'Studies Awaiting Classification' section of the review

CONTRIBUTIONS OF AUTHORS

LS: independent data extraction, review writing, data analysis and contacting study authors.

EP: independent data extraction, review writing, data analysis and contacting study authors.

JF: independent data extraction.

FS: designing search strategies, protocol development and data collection, checking of final draft.

DECLARATIONS OF INTEREST

LS: none.

EP: none.

JF: none.

FS: none.

SOURCES OF SUPPORT

Internal sources

- The University of Nottingham, UK.

Employed review author TR at time of writing protocol; however, TR wrote the protocol in her own time.
Employs FS as Cochrane Schizophrenia's Information specialist: however, FS helped with the review in his own time.
ES and JF were students at the time of writing this review.

- Hochschule Furtwangen University, Furtwangen, Germany.

Review author LS was a student as this University at the time of writing the review.

- NIHR, UK.

External sources

- National Institute for Health Research (NIHR Systematic Review Fellowship, RM-SR-2017-09-028), UK.

Grant awarded to review author LS.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We updated the methods section to reflect latest methods employed by Cochrane Schizophrenia and their methods template. We clarified that quality of life outcome for the 'Summary of findings' table would ideally be 'clinically important change' as is the case for the other outcomes.