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Asenapine versus placebo for schizophrenia (Review)

Hay A, Byers A, Sereno M, Basra MK, Dutta S

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[Intervention Review]

Asenapine versus placebo for schizophrenia

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ABSTRACT

Background

Schizophrenia is a highly prevalent and chronic disorder that comprises a wide range of symptomatology. Asenapine is a recently developed atypical antipsychotic that is approved by the US Food and Drug Administration (FDA) for the treatment of schizophrenia.

Objectives

To determine the clinical effects of asenapine for adults with schizophrenia or other schizophrenia-like disorders by comparing it with placebo.

Search methods

We searched the Cochrane Schizophrenia Group's Trials Register (July 04, 2014) which is based on regular searches of MEDLINE, EMBASE, CINAHL, BIOSIS, AMED, PubMed, PsycINFO, and registries of clinical trials. There are no language, date, document type, or publication status limitation for inclusion of records into the register. We inspected references of all included studies for further relevant studies.

Selection criteria

Our review includes randomised controlled trials (RCTs) comparing asenapine with placebo in adults (however defined) with schizophrenia or related disorders, including schizophreniform disorder, schizoaffective disorder and delusional disorder, again, by any means of diagnosis.

Data collection and analysis

We inspected citations from the searches and identified relevant abstracts, and extracted data from all included studies. For binary data we calculated risk ratio (RR) with 95% confidence intervals (CI), and for continuous data we calculated mean differences (MD). We used the GRADE approach to produce a 'Summary of findings' table which included our outcomes of interest, where possible. We used a fixed-effect model for our analyses.

Main results

We obtained and scrutinised 41 potentially relevant records, and from these we could include only six trials (n = 1835). Five of the six trials had high risk of attrition bias and all trials were sponsored by pharmaceutical companies. Results showed a clinically important change in global state (1 RCT, n = 336, RR 0.81, 95% CI 0.68 to 0.97, low-quality evidence) and mental state (1 RCT, n = 336, RR 0.72, 95% CI 0.59 to 0.86, very low-quality evidence) at short-term amongst people receiving asenapine. People receiving asenapine

demonstrated significant reductions in negative symptoms (1 RCT, n = 336, MD -1.10, 95% CI -2.29 to 0.09, very low-quality evidence) at short-term. Individuals receiving asenapine demonstrated significantly fewer incidents of serious adverse effects (1 RCT, n = 386, RR 0.29, 95% CI 0.14 to 0.63, very low-quality evidence) at medium-term. There was no clear difference in people discontinuing the study for any reason between asenapine and placebo at short-term (5 RCTs, n = 1046, RR 0.91, 95% CI 0.80 to 1.04, very low-quality evidence). No trial reported data for extrapyramidal symptoms or costs.

Authors' conclusions

There is some, albeit preliminary, evidence that asenapine provides an improvement in positive, negative, and depressive symptoms, whilst minimising the risk of adverse effects. However due to the low-quality and limited quantity of evidence, it remains difficult to recommend the use of asenapine for people with schizophrenia. We identify a need for large-scale, longer-term, better-designed and conducted randomised controlled trials investigating the clinical effects and safety of asenapine.

PLAIN LANGUAGE SUMMARY

Asenapine versus placebo for schizophrenia

Review question

Asenapine is a newer antipsychotic drug developed in the early-to-mid 1990s. The review looks at the effects of asenapine in the treatment of schizophrenia compared with placebo.

Background

People with schizophrenia often have 'positive symptoms', such as hearing voices, seeing things (hallucinations) and strange beliefs (delusions). People also have 'negative symptoms', including loss of emotions, apathy, social withdrawal, lack of pleasure and difficulty speaking and communicating. Disorder of thoughts, anxiety and depression are common. The main treatment for these symptoms of schizophrenia is antipsychotic drugs, which are divided into older drugs (typical or first generation) and newer drugs (atypical or second generation). These drugs often have severe side effects, such as weight gain, muscle stiffness, involuntary shaking and tiredness. Asenapine is a newer antipsychotic drug developed in the 1990s. At present there are no systematic reviews assessing the effects of this drug.

Study characteristics

The review includes six trials with 1835 people. The trials randomised people with schizophrenia to receive either asenapine or placebo. Five of these trials had high rates of people leaving early and were sponsored by pharmaceutical companies.

Key results

There is some evidence that asenapine, when compared to placebo, improves the positive, negative and depressive symptoms of schizophrenia while having less risk of debilitating side effects.

Quality of the evidence

However, due to the low quantity and limited quality of evidence currently available, it remains difficult to recommend the use of asenapine for schizophrenia. There is a need for large-scale, longer-term follow up, and bias-free randomised controlled trials investigating the effects and safety of asenapine.

Ben Gray, Senior Peer Researcher, McPin Foundation. http://mcpin.org/

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

ASENAPINE versus PLACEBO for schizophrenia

Patient or population: adults with schizophrenia
Settings: inpatient and outpatient
Intervention: ASENAPINE versus PLACEBO

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	ASENAPINE versus PLACEBO				
Global state: No clinically important change CGI-I Follow-up: up to 12 weeks	**Study population**		**RR 0.81** (0.68 to 0.97)	336 (1 study)	⊕⊕◯◯ **low**[1,2,3]	
	664 per 1000	**538 per 1000** (451 to 644)				
	Moderate					
	664 per 1000	**538 per 1000** (452 to 644)				
Mental state: No clinically important change PANSS Follow-up: up to 12 weeks	**Study population**		**RR 0.72** (0.59 to 0.86)	336 (1 study)	⊕◯◯◯ **very low**[1,2,3,4]	
	672 per 1000	**484 per 1000** (397 to 578)				
	Moderate					
	672 per 1000	**484 per 1000** (396 to 578)				

Mental state: Average change score in negative symptoms PANSS Marder negative factor score Follow-up: up to 12 weeks	The mean mental state: average change score in negative symptoms in the intervention groups was **1.1 lower** (2.29 lower to 0.09 higher)			336 (1 study)	⊕○○○ **very low**[1,2,3,4]
Adverse effects: Incidence of serious adverse effects Follow-up: 13-26 weeks	**Study population**		**RR 0.29** (0.14 to 0.63)	386 (1 study)	⊕○○○ **very low**[2,3,5,6,7]
	141 per 1000	**41 per 1000** (20 to 89)			
	Moderate				
	141 per 1000	**41 per 1000** (20 to 89)			
Adverse effects: Clinically significant extrapyramidal symptoms AIMS Follow-up: 13-26 weeks	No trial reported this outcome.				
Leaving the study early - any reason Follow-up: up to 12 weeks	**Study population**		**RR 0.91** (0.80 to 1.04)	1046 (5 studies)	⊕○○○ **very low**[10,11,12]
	488 per 1000	**444 per 1000** (390 to 507)			
	Moderate				
	484 per 1000	**440 per 1000** (387 to 503)			
Economic costs	No trial reported this outcome.				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Risk of bias: 'Very serious' - Random sequence generation, allocation concealment and blinding (participants/personnel and outcome assessment) are poorly described.
[2] Risk of bias: 'Very serious' - Attrition bias (method of analysis for dealing with incomplete data was last observation carried forward) and other bias (association with and funded by pharmaceutical companies) were sources of high risk.
[3] Inconsistency: 'No' - Only one study.
[4] Indirectness: 'Serious' - Marder factor scores determined using factor analysis of PANSS items.
[5] Risk of bias: 'Very serious' - Random sequence generation and allocation concealment are poorly described.
[6] Risk of bias: 'Very serious' - Blinding of outcome assessment (possibility of biased judgement) and reporting bias (insufficient data reported for certain outcomes) were sources of high risk.
[7] Imprecision: 'Serious' - Low event rate.
[8] Indirectness: 'Serious' - AIMS specifically assesses tardive dyskinesia.
[9] Imprecision: 'Serious' - Wide confidence interval.
[10] Risk of bias: 'Very serious' - Blinding of participants/personnel (four of five studies), attrition bias (four of five studies), selective reporting (four of five studies) and other bias (all five studies) were sources of high risk.
[11] Inconsistency: 'Serious' - This outcome had moderate levels of heterogeneity due to one study (I^2 = 43%).
[12] Imprecision: 'No' - Large event rate and sample with a narrow confidence interval.

BACKGROUND

Description of the condition

Schizophrenia affects approximately 0.3% to 0.7% of people during their lifetime, with an estimated 24 million individuals experiencing the disorder worldwide (McGrath 2008; WHO 2014). With similar prevalence and incidence rates globally, it is widely accepted that schizophrenia is associated with significant global burden (Ayuso-Mateos 2006). The prevalence rates of schizophrenia are similar for men and women (Saha 2005). With a considerably variable age of onset, schizophrenia can present for the first time from adolescence, through middle age (late-onset schizophrenia), and up to old age (very late-onset schizophrenia-like psychosis) (Kohler 2007). It has been established that an interaction of multiple genetic and environmental factors are involved in the aetiology of schizophrenia (van Os 2008). Such heterogeneous aetiology may contribute to the diverse illness course and symptomatology seen in the disease (Andreasen 1999; Walker 2004).

Schizophrenia is typically considered in relation to the dichotomy of positive symptoms such as delusions and hallucinations, which are characterised by their atypical presence; and negative symptoms, such as poverty of speech, flattened affect, lack of pleasure (anhedonia), and lack of motivation (avolition) (Crow 1980). Moreover, patients with schizophrenia can express a disorganised state primarily marked by disorganised thought and speech, known as formal thought disorder (Liddle 1987). Mood symptoms such as depression and anxiety are also very common in schizophrenia yet are heterogeneous in nature and so require thorough investigation (Siris 2000). Furthermore, there is increasing evidence that people with schizophrenia exhibit deficits in several domains of cognitive functioning including memory, language, executive functioning and attention (Fioravanti 2005).

Description of the intervention

Antipsychotic drugs are used as first-line medication for schizophrenia. Typical (or first-generation) antipsychotics, such as chlorpromazine and haloperidol, have been available since the 1950s, whilst atypical (or second-generation) antipsychotics, such as clozapine and olanzapine, have been introduced from the late 1980s (Lehmann 1997). Atypical antipsychotics have been marked as producing greater reductions in negative and mood symptoms, whilst minimising adverse effects usually observed during typical antipsychotic treatment, such as extrapyramidal symptoms and hyperprolactinaemia (Davis 2003; Worrel 2000). However, atypical antipsychotics are not without their own adverse effects including sedation, sexual dysfunction, weight gain, diabetes, and cardiovascular problems (Muench 2010).

Asenapine is a novel second-generation antipsychotic originally developed by Organon in the early-to-mid 1990s, which was approved by the US Food and Drug Administration (FDA) in 2009 for the acute treatment of adults with schizophrenia and bipolar I disorder (Citrome 2009). However, in the European Union and the UK it is currently approved for the acute treatment of bipolar I disorder only and not for schizophrenia (EMA 2014).

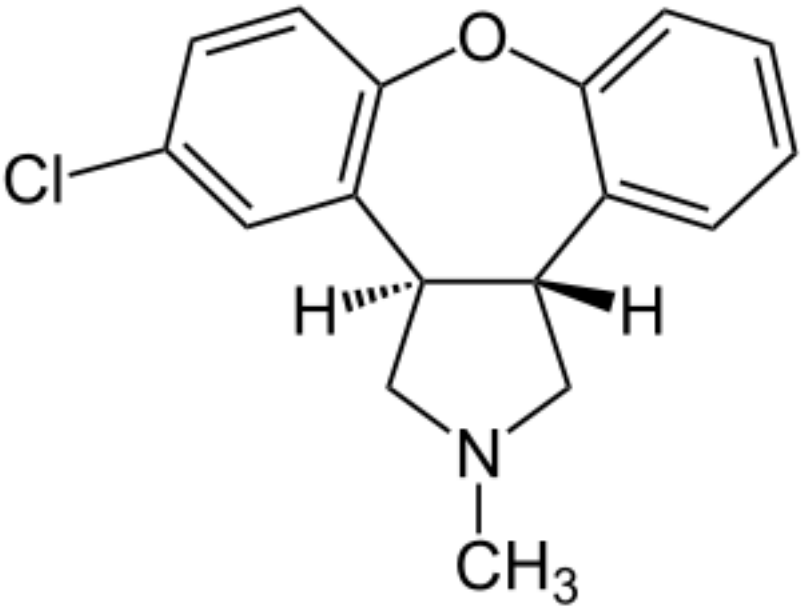
Initial investigation of the properties and clinical effects of asenapine has begun (Stoner 2012), although the use of placebo-controlled clinical trials can be difficult to justify, particularly when evidence-based pharmacological treatments for schizophrenia already exist (Emsley 2013). However, aside from investigating the comparative effects of novel antipsychotic drugs with others that are currently available, it is important to consider the absolute effects of medication purported to be antipsychotic (Storosum 1998).

How the intervention might work

Asenapine is predominantly administered sublingually (5 mg to 10 mg twice daily) due to previous reports of low bioavailability when administered orally, and typically reaches peak plasma levels within 30 to 90 minutes following absorption via the oral mucosa (FDA 2013).

Asenapine is a novel second-generation antipsychotic drug (see Figure 1 for its chemical structure). It has a somewhat unique pharmacological profile compared to alternative atypical antipsychotic medication and has a greater affinity for a range of serotonergic, dopaminergic, noradrenergic, and histamine receptors, acting through the antagonism of most of these receptor subtypes, whilst expressing low affinity to muscarinic receptors (Shahid 2009). It has been proposed that antagonism of dopamine and noradrenergic receptors contributes substantially to the alleviation of positive symptoms in schizophrenia (Abi-Dargham 2004; Svensson 2003). Additionally, the antagonism of serotonergic receptors may improve negative, cognitive and mood symptoms of schizophrenia (Hedlund 2004; Meltzer 1999).

Figure 1. Chemical structure of asenapine



With its low affinity to muscarinic receptors, asenapine may minimise the risk of anticholinergic adverse effects reported following the use of some antipsychotic drugs (Lieberman 2004). However, histamine antagonism is known to produce sedation (Nicholson 1983), which is one of several adverse effects that have been identified following the use of asenapine, in addition to anxiety, extrapyramidal symptoms, nausea/vomiting, oral hypoesthesia, and weight gain (Sycrest 2014).

Why it is important to do this review

It is well known that both typical and atypical antipsychotics can be costly and have an assorted adverse event profile, yet they still do not fully meet the treatment needs of people with schizophrenia (Campbell 1999). As asenapine is one of the more recently developed second-generation antipsychotic drugs with multi-targeted pharmacological action, it has been suggested that it may have the potential to produce clinical improvements in negative and cognitive symptoms, as well as positive symptoms of schizophrenia, whilst minimising the incidence of adverse effects (Bishara 2009). At present there are no systematic reviews assessing the clinical effects of asenapine, although there are two currently underway comparing asenapine to typical antipsychotics and other atypical antipsychotics (Kumar 2012; Preda 2010). Therefore, the purpose of this systematic review is to summarise evidence from randomised controlled trials comparing the clinical effects and safety of asenapine to placebo amongst adults with schizophrenia and other schizophrenia-like disorders.

OBJECTIVES

To determine the clinical effects of asenapine for adults with schizophrenia or other schizophrenia-like disorders by comparing it with placebo.

METHODS

Criteria for considering studies for this review

Types of studies

All relevant randomised controlled trials (RCTs). If a trial had been described as 'double-blind' and implied that randomisation occurred but did not state it overtly, we intended to include it in a sensitivity analysis (see Sensitivity analysis). If inclusion of such trials did not result in a substantive difference, they were to remain in the analyses. If their inclusion resulted in important clinically significant (but not necessarily clear differences), we would not add the data from these lower quality studies to the results of the better trials, but present such data within a subcategory. We excluded quasi-randomised studies, such as those that allocate to treatment groups by alternate days of the week. Where people are given additional treatments within asenapine, we only included the data if the adjunct treatment was evenly distributed between groups and only asenapine was randomised.

Types of participants

Adults with schizophrenia or related disorders, however defined, including schizophreniform disorder, schizoaffective disorder and delusional disorder, again, by any means of diagnosis. Where trials included participants with a range of disorders we only included trials where over 50% of the participants have schizophrenia.

We are interested in making sure that information is as relevant to the current care of people with schizophrenia as possible, so where information was available we highlighted clearly the current clinical state of participants (acute, early post-acute, partial remission, remission) as well as the stage (prodromal, first episode, early illness, persistent) and whether the studies primarily focused on people with particular problems (for example, negative symptoms, treatment-resistant illnesses).

Types of interventions

1. Asenapine

Any dose, any method of administration.

2. Placebo

Any method of administration.

Types of outcome measures

Where possible, we divided outcomes into short-term (up to 12 weeks), medium-term (13 weeks to 26 weeks) and long-term (over 26 weeks).

Primary outcomes

1. Global state

1.1 Clincally important change in global state as defined by each study

2. Mental state

2.1 Clinically important change in mental state as defined by each study

3. Adverse effects

3.1 Incidence of serious adverse effects

Secondary outcomes

1. Global state

1.1 Average endpoint in global state
1.2 Average change in global state (baseline to endpoint)
1.3 Relapse as defined by each study
1.4 Use of any concomitant medication
1.4.1 Use of specific concomitant medication
1.5 Adherence to trial medication

2. Mental state

2.1 General symptoms
2.1.1 Average endpoint in general mental state score
2.1.2 Average change in general mental state score (baseline to endpoint)
2.2 Average endpoint in specific symptoms
2.2.1 Positive symptoms (delusions, hallucinations)
2.2.2 Negative symptoms (avolition, poor self care, blunted affect)
2.2.3 Mood (anxiety, depression, mania)
2.2.4 Other psychotic symptoms (e.g. disorganised thought)
2.3. Average change in specific symptoms (positive, negative, mood, other symptoms, baseline to endpoint)

3. Cognitive functioning

3.1 General cognitive functioning as defined by each study
3.1.1 Clinically important change in general cognitive functioning as defined by each study
3.1.2 Average endpoint in general cognitive functioning
3.1.3 Average change in general cognitive functioning (baseline to endpoint)
3.2 Specific cognitive functioning as defined by each study
3.2.1 Clinically important change in specific cognitive functioning as defined by each study
3.2.2 Average endpoint in specific cognitive functioning
3.2.3 Average change in specific cognitive functioning (baseline to endpoint)

4. Behaviour

4.1 General behaviour as defined by each study
4.1.1 Clinically important change in general behaviour as defined by each study
4.1.2 Average endpoint in general behaviour
4.1.3 Average change in general behaviour (baseline to endpoint)
4.2 Specific behaviour as defined by each study
4.2.1 Clinically important change in specific behaviour as defined by each study
4.2.2 Average endpoint in specific behaviour
4.2.3 Average change in specific behaviour (baseline to endpoint)

5. Functioning

5.1 General functioning as defined by each study
5.1.1 Clinically important change in general functioning as defined by each study
5.1.2 Average endpoint in general functioning
5.1.3 Average change in general functioning (baseline to endpoint)

5.2 Specific functioning as defined by each study
5.2.1 Clinically important change in specific functioning as defined by each study
5.2.2 Average endpoint in specific functioning
5.2.3 Average change in specific functioning (baseline to endpoint)

6. Adverse effects

6.1 Incidence of any adverse effects
6.1.1 Incidence of adverse effects by severity as defined by each study (excluding serious adverse effects)
6.2 Incidence of other specific adverse effects as defined by each study
6.3 Extrapyramidal symptoms
6.3.1 Incidence of extrapyramidal symptoms
6.3.2 Clinically important extrapyramidal symptoms as defined by each study
6.3.3 Average score/change in extrapyramidal symptoms
6.4 Deaths, by suicide or natural causes

7. Leaving the study early - for any reason

8. Service utilisation outcomes

8.1 Hospital admissions
8.2 Days in hospital

9. Quality of life

9.1 Clinically important change in quality of life
9.2 Average endpoint in quality of life
9.3 Average change in quality of life (baseline to endpoint)

10. Economic outcomes

'Summary of findings' table

We used the GRADE approach to interpret findings (Schünemann 2011), and use GRADEPRO profiler to import data from RevMan 5 (Review Manager) to create a 'Summary of findings' table. This table provides outcome-specific information concerning the overall quality of evidence from each included study in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on all outcomes we rate as important to patient-care and decision making. We selected the following main outcomes for inclusion in Summary of findings for the main comparison:

- Global state - clinically important change in global state as defined by each study
- Mental state - clinically important change in mental state as defined by each study
- Mental state - average change in negative symptoms
- Adverse effects - incidence of serious adverse effects
- Adverse effects - clinically significant extrapyramidal symptoms
- Leaving the study early - for any reason
- Economic outcome

Search methods for identification of studies

Electronic searches

The Trials Search Coordinator (TSC) searched the Cochrane Schizophrenia Group's Trials Register (04 July, 2014) using the following search strategies:
((Saphris or "ORG 5222" or asenapine) and placebo) in Title or Abstract Fields of REFERENCE Records or (asenapine and placebo) in Intervention Fields of STUDY Records.
The Cochrane Schizophrenia Group's Trials Register is compiled by systematic searches of major resources (including MEDLINE, EMBASE, AMED, BIOSIS, CINAHL, PsycINFO, PubMed, and registries of clinical trials) and their monthly updates, handsearches, grey literature, and conference proceedings (see Group Module). There are no language, date, document type, or publication status limitation 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

If necessary we contacted the first author, relevant pharmaceutical companies, and drug approval agencies of trials for additional information. We noted the outcome of this contact in the included or awaiting assessment studies tables.

Data collection and analysis

Selection of studies

AH, AB, MS, MB, SD and IJ independently inspected citations from the searches and identified relevant abstracts. A random 20% sample was independently re-inspected by AH, AB, MS, MB and

SD to ensure reliability. If disputes arose, we acquired the full report for more detailed scrutiny. AH, AB, MS, MB and SD obtained and inspected full reports of the abstracts meeting the review criteria. Again, AH, AB, MS, MB and SD re-inspected a random 20% of reports in order to ensure reliable selection. If it was not possible to resolve disagreement by discussion, we attempted to contact the authors of the study for clarification.

Data extraction and management

1. Extraction

Review authors AH and AB extracted data from all included studies. In addition, to ensure reliability, MS independently extracted data from a random sample of these studies, comprising 10% of the total. Again, any disagreement was discussed, decisions documented and, if necessary, authors of studies contacted for clarification. We extracted data presented only in graphs and figures whenever possible, but we only included these data if two reviewers independently obtained the same result. We attempted to contact authors through an open-ended request in order to obtain missing information or for clarification whenever necessary. For multi-centred studies, where possible, we extracted data relevant to each component centre separately.

2. Management

2.1 Forms

We extracted data onto standard, pre-designed 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); and
- the measuring instrument had not been written or modified by one of the trialists for that particular trial.

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

2.3 Endpoint versus change data

There are advantages of both endpoint and change data. Change data can remove a component of between-person variability from the analysis, however, calculation of change needs two assessments (baseline and endpoint) which can be difficult to achieve in unstable and difficult-to-measure conditions such as schizophrenia. We decided primarily to use endpoint data, and only use change data if the former were not available. We combined endpoint and change data in the analysis as we prefered to use mean differences (MD) rather than standardised mean differences throughout (Higgins 2011a).

2.4 Skewed data

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

For large studies and change data

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

For endpoint data from smaller studies (< 200)

- When a scale starts from the nite number zero, we subtracted the lowest possible value from the mean, and divided this by the standard deviation. If this value is lower than one, it strongly suggests a skew and we excluded the study data. If this ratio is higher than one but below two, there is suggestion of skew. We entered the study data and tested whether its inclusion or exclusion would change the results substantially. Finally, if the ratio is larger than two we included the study data, because skew is less likely (Altman 1996; Higgins 2011a).
- 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 converted, where relevant, variables that can be reported in different metrics, such as days in hospital (mean days per year, per week or per month) to a common metric (e.g. mean days per month).

2.6 Conversion of continuous to binary

Where possible, we made efforts 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 Positive and Negative Syndrome Scale (PANSS) (Kay 1986), this could be considered as a clinically significant response (Leucht 2005). 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 indicates a favourable outcome for asenapine. Where keeping to this makes it impossible to avoid outcome titles with clumsy double-negatives (e.g. 'Not un-improved') we reported data where the left of the line indicates an unfavourable outcome. We noted this in the relevant graphs.

Assessment of risk of bias in included studies

Again review authors AB, SD and MS, worked independently to assess risk of bias by using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess trial quality (Higgins 2011b). This set of criteria is based on evidence of associations between overestimate of effect and high risk of bias of the article such as sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting.

If the raters disagreed, we made the final rating by consensus, with the involvement of another member of the review group. Where inadequate details of randomisation and other characteristics of trials are provided, we attempted to contact the authors of the studies in order to obtain further information. If there was non-concurrence in quality assessment we would have reported this, and if disputes had arisen regarding the category to which a trial was to be allocated, again, we would have resolved by discussion. We noted the level of risk of bias in both the text of the review and in the 'Summary of findings' table.

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 than odds ratios (Boissel 1999), and that odds ratios tend to be interpreted as RR by clinicians (Deeks 2000). The number needed to treat for an additional beneficial outcome (NNTB)/number needed to treat for an additional harmful outcome (NNTH) statistic with its confidence intervals is intuitively attractive to clinicians but is problematic both in its accurate calculation in meta-analyses and interpretation (Hutton 2009). For binary data presented in Summary of findings for the main comparison, where possible, we calculated illustrative comparative risks.

2. Continuous data

For continuous outcomes we estimated mean difference (MD) between groups. We prefered not to calculate effect size measures (standardised mean difference (SMD)). However, if scales of very considerable similarity had been used, we would have presumed there was a small difference in measurement, and we 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. Firstly, authors often fail to account for intra-class correlation in clustered studies, leading to a 'unit of analysis' error whereby P values are spuriously low, confidence intervals unduly narrow and statistical significance overestimated (Divine 1992). This causes type I errors (Bland 1997; Gulliford 1999).

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

We have sought statistical advice and were advised that the binary data 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 intra-class correlation coefficient (ICC) [Design effect = 1 + (m - 1) *ICC] (Donner 2002). If the ICC is not reported it will be assumed to be 0.1 (Ukoumunne 1999).

If cluster studies are appropriately analysed taking into account intra-class correlation coefficients and relevant data documented in the report, synthesis with other studies will be possible using the generic inverse variance technique.

2. Cross-over trials

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

3. Studies with multiple treatment groups

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

Dealing with missing data

1. Overall loss of credibility

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

2. Binary

When attrition for a binary outcome is between 0% and 50%, and where these data are not clearly described, we presented data on a 'once-randomised-always-analyse' basis (an intention-to-treat analysis). We assumed those leaving the study early to have the same rates of negative outcome as those who completed the study, 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 intended, if possible, to undertake a sensitivity analysis testing how prone the primary outcomes are to change when data only from people who complete the study to that point are compared to the intention-to-treat analysis using the above assumptions.

3. Continuous

3.1 Attrition

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

3.2 Standard deviations

If standard deviations were not reported, we first tried to obtain the missing values from the authors. If these were not available, where there are missing measures of variance for continuous data, but an exact standard error and confidence intervals are available for group means, and either P value or 't' value are available for differences in the mean, we calculated them according to the rules described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). When only the standard error (SE) is reported, standard deviations (SDs) can be calculated by the formula SD = SE * square root (n). Chapters 7.7.3 (Higgins 2011a) and 16.1.3 (Higgins 2011c) of the *Cochrane Handbook for Systematic Reviews of Interventions* present detailed formulae for estimating SDs from P values, t or F values, CIs, ranges or other statistics. If these formulae do not apply, we calculated the SDs according to a validated imputation method based on the SDs of the other included studies (Furukawa 2006). Although some of these imputation strategies can introduce error, the alternative would be to exclude a given study's outcome and thus to lose information. We intended to examine 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 trials early or are lost to follow-up. Some trials present only 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 common. While the latter methods seem to be somewhat better than LOCF (Leon 2006), we feel that the high percentage of participants leaving the studies early and differences in the reasons for leaving the studies between groups is often the core problem in randomised schizophrenia trials. We therefore did not exclude studies based on the statistical approach used. We prefered to use the more sophisticated approaches. e.g. MMRM or multiple-imputation to LOCF, and completer analysis was only presented if some kind of intention-to-treat data were not available at all. Moreover, we addressed this issue in the item 'incomplete outcome data' in the risk of bias tool.

Assessment of heterogeneity

1. Clinical heterogeneity

Initially we considered all included studies, without seeing comparison data, to judge clinical heterogeneity. We simply inspected all studies for clearly outlying people or situations that we had not predicted would arise. We discussed any such situations or participant groups when they arose.

2. Methodological heterogeneity

Initially we considered all included studies, without seeing comparison data, to judge methodological heterogeneity. We simply inspected all studies for clearly outlying methods that we had not predicted would arise. We discussed any methodological outliers.

3. Statistical heterogeneity

3.1 Visual inspection

We inspected graphs visually 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 provides an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of I^2 depends firstly on magnitude and direction of effects and secondly on the strength of evidence for heterogeneity (e.g. P value from Chi^2 test, or a confidence interval for I^2). An I^2 estimate greater than or equal to around 50% accompanied by a statistically significant Chi^2 statistic, is interpreted as evidence of substantial levels of heterogeneity (*Cochrane Handbook for Systematic Reviews of Interventions* Section 9.5.2; Deeks 2011). If substantial levels of heterogeneity were found in the primary outcome, we would have explored reasons for heterogeneity (Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

1. Protocol versus full study

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results. These are described in section 10.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We tried to locate protocols of included randomised trials. If the protocol was available, we compared outcomes in the protocol and in the published report. If the protocol was not available, we compared outcomes listed in the methods section of the trial report with the results actually reported.

2. Funnel plot

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

Data synthesis

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

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

1.1 Primary outcomes

To treat schizophrenia, asenapine is currently administered twice a day in a 5 mg or 10 mg dose (FDA 2013). We intended to conduct a subgroup analysis by asenapine dose (5 mg twice a day versus placebo, 10 mg twice a day versus placebo) on any primary outcome where there was significant heterogeneity (defined as $I^2 \leq 75$; Higgins 2011a). We did not anticipate any subgroup analyses concerning the form of administration of asenapine as it is predominantly administered sublingually (FDA 2013).

1.2 Clinical state, stage or problem

We proposed to undertake this review and provide an overview of the effects of asenapine for people with schizophrenia in general. In addition we intended, if possible, 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 is high. Firstly we investigated whether data had been entered correctly. Secondly, if data were correct, we inspected the graph visually and successively removed outlying studies to see if homogeneity was restored. For this review we decided that should this occur with data contributing no more than around 10% of the total weighting to the summary finding, data were to be presented. If not, data would have been pooled and issues discussed. We know of no supporting research for this 10% cut off, but are investigating use of prediction intervals as an alternative to the current unsatisfactory state.

When unanticipated clinical or methodological heterogeneity is obvious we will simply state hypotheses regarding them for future reviews or versions of this review. We do not anticipate undertaking analyses relating to unanticipated clinical or methodological heterogeneity.

Sensitivity analysis

1. Implication of randomisation

We aimed, if possible, to include trials in a sensitivity analysis if they were described in some way that implied 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 description of randomisation, then all data from these studies would have been employed.

2. Assumptions for lost binary data

If assumptions had to be made regarding people lost to follow-up (see Dealing with missing data) we would have compared the findings of the primary outcomes when we used our assumptions and when we used data only from people who completed the study to that point. If there had been a substantial difference, we would have reported results and discussed them, but continued to employ our assumption.

For continuous data, if assumptions had to be made regarding missing SDs (see Dealing with missing data), we would have compared the findings of the primary outcomes when we used our assumptions and when we used data only from people who completed the study to that point. A sensitivity analysis would have been undertaken testing how prone results are to change when completer-only data are compared to the imputed data using the above assumption. If there is a substantial difference, we would have reported results and discussed them, but continued to employ our assumption.

3. Risk of bias

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

4. Imputed values

We also, if required, intended 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.

5. Fixed-effect and random-effects

All data were synthesised 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

RESULTS

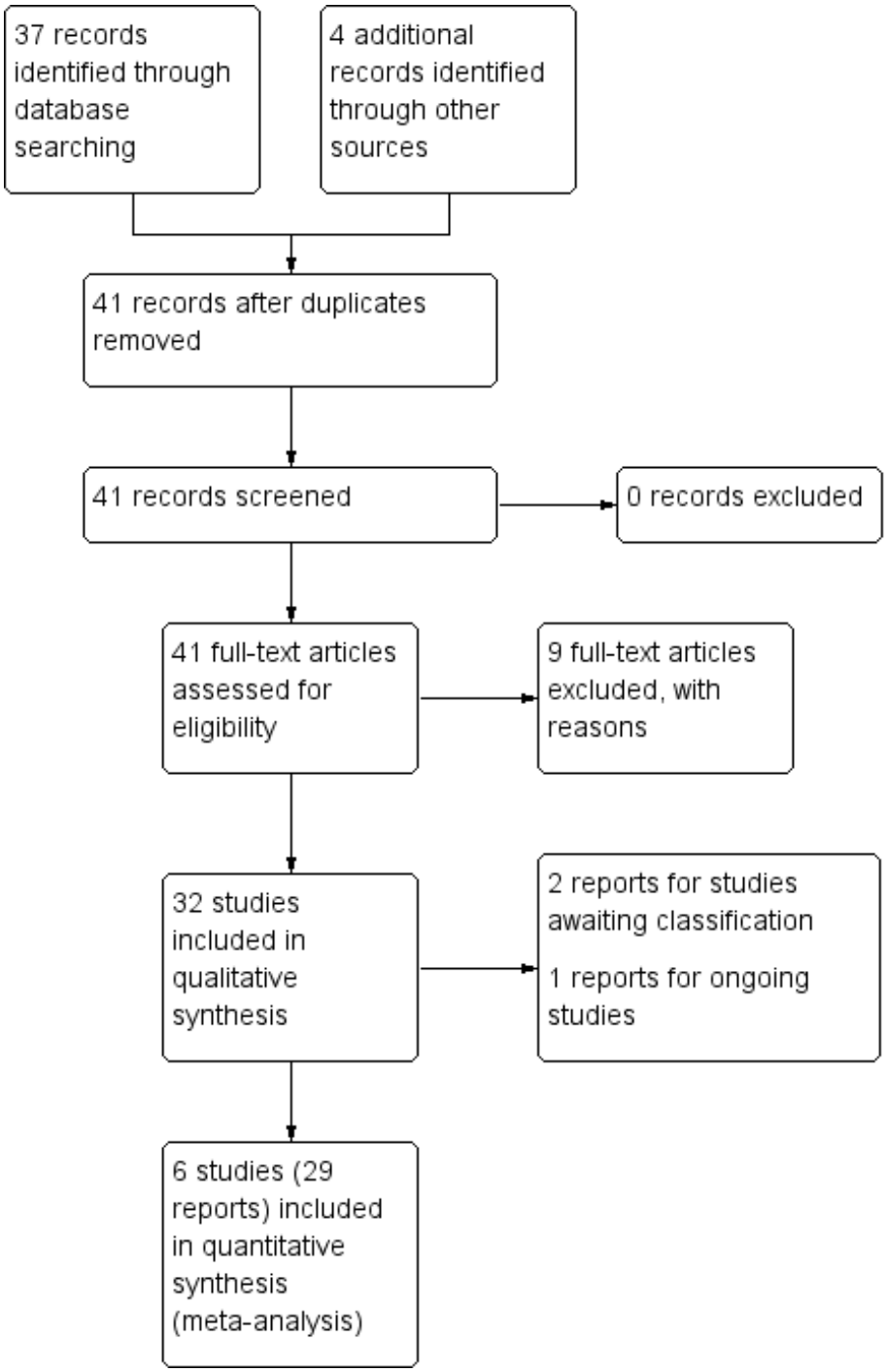
Description of studies

For in-depth descriptions of the studies please see Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; and Characteristics of ongoing studies.

Results of the search

Electronic searches identified 37 references with 4 additional records identified through other sources. After duplicates were removed, we screened 41 records and nine of these reports (seven trials) did not meet the inclusion criteria (see Characteristics of excluded studies) and had to be excluded. Additionally, two trials (two reports) are awaiting classification, and one trial (one report) is currently ongoing. Six trials (29 reports) are included (Figure 2).

Figure 2. Study flow diagram.



Included studies

1.1 Methods

The six included studies were explicitly described as randomised (Chapel 2009; Kane 2011; NCT00151424; Kane 2010; NCT00156117; Potkin 2007). Six weeks was a common trial length (Kane 2010; Potkin 2007) and the duration varied from the shortest trial lasting 16 days (Chapel 2009) and the longest trial lasting 52 weeks (Kane 2011).

1.2 Setting

Three trials involved inpatients and outpatients (NCT00151424; Kane 2010; Potkin 2007), The settings of the other studies were not clearly specified.

1.3 Participants

All studies reported participants to have schizophrenia or schizoaffective disorder using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) or DSM-IV Text Revision (DSM-IV-TR). Data from 1835 people are included in the review.

1.4 Study size

The mean number of participants in each trial was 305, ranging from 148 (Chapel 2009) to 458 (Kane 2010).

1.5 Interventions

1.5.1 Asenapine
The dose of asenapine ranged from 5mg to 20mg twice a day (BID). Asenapine was administered sublingually.
1.5.2 Placebo
All trials compared asenapine with placebo which were indistinguishable from each other. Placebo was administered orally or sublingually.
1.5.3 Other drug treatment arms
Five of the the trials included one more intervention arm along with placebo and asenapine. These were quetiapine (Chapel 2009), risperidone (Potkin 2007), olanzapine (NCT00151424; NCT00156117), and haloperidol (Kane 2010). The data for these arms were not included in the review.

1.6 Outcomes

The outcomes reported by included studies were global state, mental state, adverse effects and leaving the study early. None of the included studies had any evidence of the clinical effects of asenapine/placebo on cognitive functioning, behaviour, functioning, service utilisation, quality of life, or reported economic data.
The following scales were used and provided data for the analysis.

1.6.1 Global state

The Clinical Global Impression rating scales are used in various mental disorders in order to quantify symptom severity, treatment response and efficacy of treatment.
1.6.1.1 Clinical Global Impression (CGI) (Guy 1976)
A scale (seven points) is used in which clinicians are required to rate the severity of the patient's illness, with higher scores indicating increased severity/reduced recovery. This measure requires the clinician to use all available information including the history of the patient, symptoms, social environment and impact on the patient's functioning.

1.6.1.2 Clinical Global Impression - Severity of Illness (CGI-S)

A sub-scale of the CGI which requires clinicians to rate the current severity of the patient's illness compared to the clinician's past experience with patients. Mental illness is assessed on a seven-point scale, scores ranging from one to seven, where a higher score indicates a higher severity of illness.

1.6.1.3 Clinical Global Impression - Improvement (CGI-I)

A sub-scale of the CGI which requires the clinicians to rate the extent to which the patient's illness has deteriorated or improved in comparison with a baseline state at the start of the intervention. Again this uses a seven-point scale, scores ranging from one to seven. A score of one indicates 'very much improved', four indicates 'no change', and seven indicates 'very much worse'.

1.6.2 Mental state

1.6.2.1 Positive and Negative Syndrome Scale (PANSS) (Kay 1987)
This is widely used in the form of a clinical interview with patients with schizophrenia to measure the severity of their symptoms. The interview items include three sub-scales, positive (seven items), negative (seven items) and general psychopathology (16 items) whereby patients are rated from one to seven on the 30

different symptoms. Therefore the lowest a patient can score on the PANSS scale is 30. A higher score indicates a higher severity of illness. The first two scales refer to the positive (hallucinations/ delusions) and negative (blunted effect/social and emotional withdrawal) symptoms of schizophrenia. The general psychopathology scale includes 16 items of which some include anxiety/guilt feelings, tension, mannerisms, depression and motor retardation. Often scores are given separately for the three different scales.

An alternative approach to scoring the PANSS is through the use of clinician-rated Marder factor sub-scales (Marder 1997). Following factor analysis of the PANSS, five symptom dimensions were identified. The sub-scales include positive symptoms (eight items; score range of 8 - 56); negative symptoms (seven items; score range of 7 - 49); disorganized thought (seven items; score range of 7 - 49); hostility/excitement (four items; score range of 4 - 28); and anxiety/depression (four items; score range of 4 - 28).

1.6.2.2 Calgary Depression Scale for Schizophrenia (CDSS) (Addington 1993)

This clinician-rated scale is used in order to assess depressive symptoms, usually in the form of a semi-structured interview, with patients with schizophrenia. The items on the scale include depressed mood, guilt (delusions/ pathological), hopelessness, low self-esteem, observed depression, weight loss, disrupted sleep and suicide. Scores range from 0 - 4, where a higher score indicates higher severity of depression.

1.6.3 Adverse effects

1.6.3.1 Abnormal Involuntary Movement Scale (AIMS) (Munetz 1988)

A clinician-rated scale used to assess the severity of tardive dyskinesia, particularly in patients taking neuroleptic medications. There are 12 Items, with scores ranging from zero to four, assessing facial movements, global severity, extremities, trunk movements and dental status. A higher score indicates higher severity.

1.6.3.2 Simpson - Angus Scale (SAS) (Simpson 1970)

A ten-item clinician-rated scale which assesses neuroleptic-induced Parkinsonism (NIP) in schizophrenia. Signs assessed include head dropping, shoulder shaking, salivation, tremors and elbow/wrist rigidity. A five-point scale with scores ranging from 0 - 40 is used to assess the severity, the higher the score the more severe NIP.

1.6.3.3 Barnes Akathisia Scale (BAS) (Barnes 1989)

A clinician-rated rating scale in which drug-induced akathisia severity is assessed. Items assess the frequency and objective presence of akathisia, the individual's awareness and distress, and the global severity. The objective and subjective ratings are scored from zero to three where a higher score indicates higher severity of restlessness, awareness of restlessness and distress related to restlessness. A six-point scale is used to assess global severity with scores ranging from zero to five, a higher score specifies higher severity.

Excluded studies

Seven studies were excluded in this review. These are listed in the Characteristics of excluded studies table. Three of the studies were not randomised (Castle 2013; Leucht 2013; The National Horizon Scanning Centre 2010). A further three did not have a placebo control (Cazorla 2008; NCT00156065; NCT01142596). Since we are only including studies with adult participants we excluded NCT01190254 as this focused on adolescents.

Studies awaiting classification

NCT00156091 and NCT01098110 meet our inclusion criteria and would have been listed in the included studies if sufficient information had been available. NCT01098110 has been recently completed (April 2014). It is possible that their data analysis has been completed since the time of writing and we will add this information to future versions of this review if it is available.

Ongoing studies

One ongoing study has been identified (NCT01617187). This randomised study was started in December 2012 and is estimated to include 354 adults with schizophrenia. The study assesses the effects of two doses of asenapine (2.5 mg and 5 mg BID) versus placebo on global and mental state in a six-week trial. The estimated date of completion for the study is September 2014. This trial is being sponsored by Merck.

Risk of bias in included studies

Information for risk of bias across the included studies is illustrated in Figure 3 and Figure 4.

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

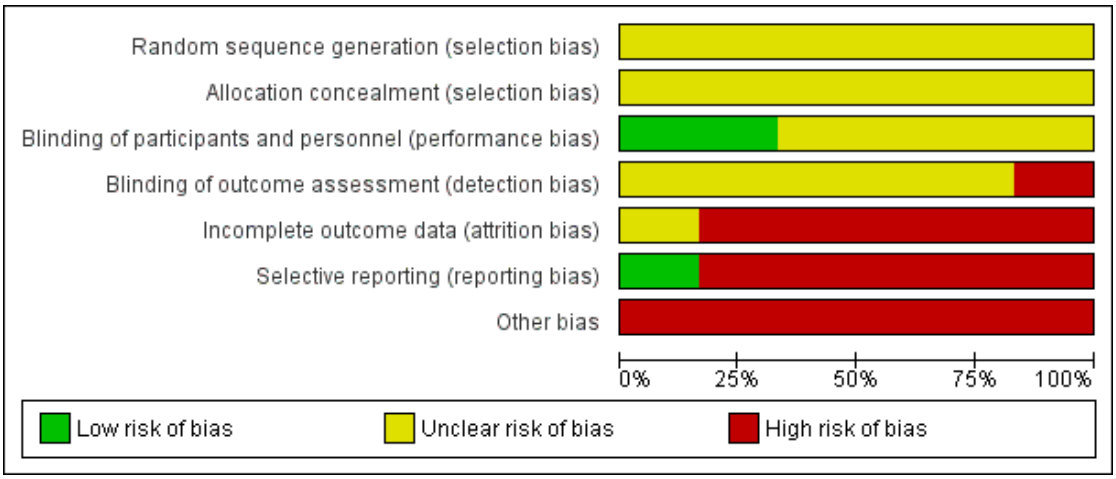
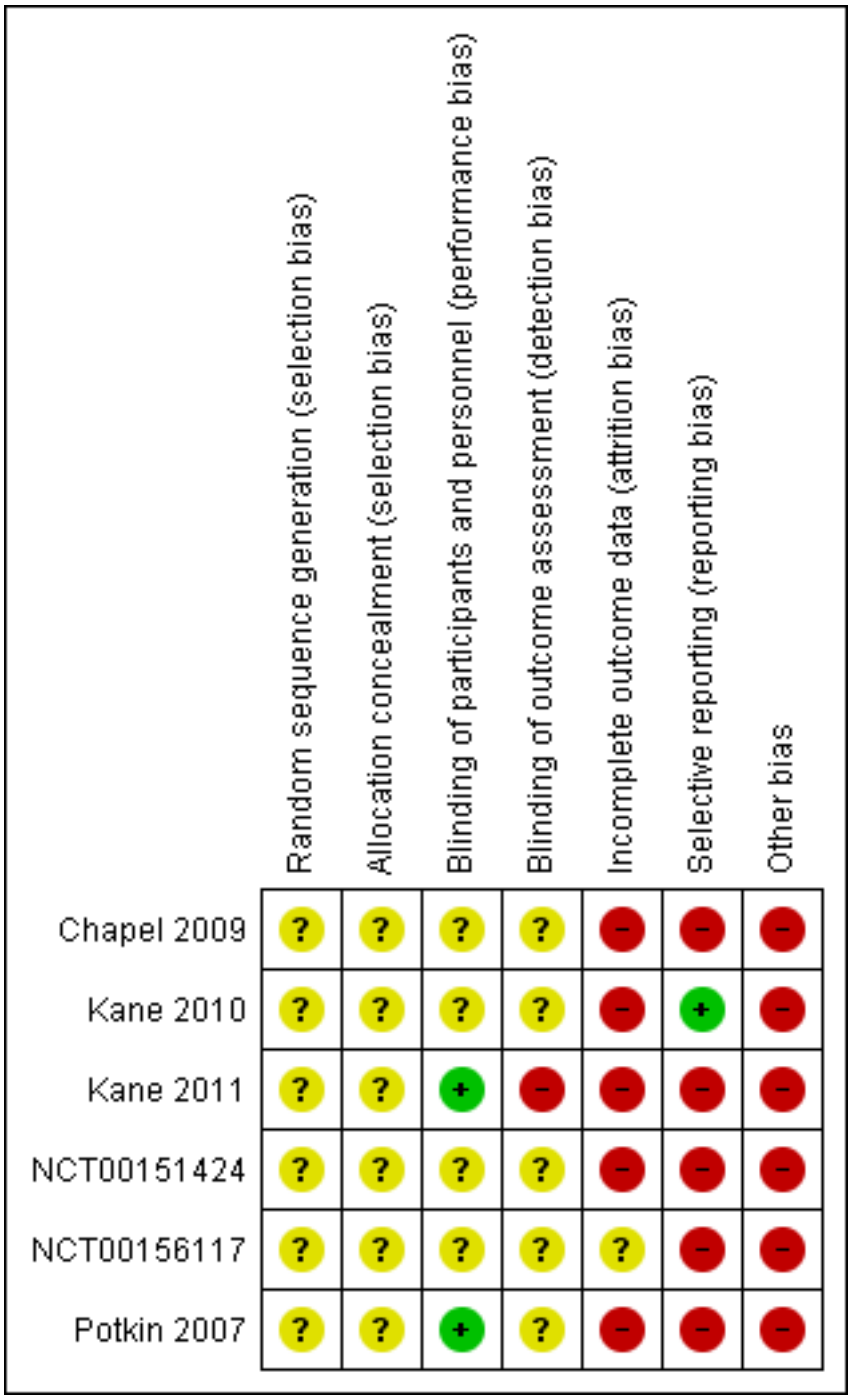


Figure 4. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The six studies do not explicitly describe the method used for randomisation of participants, although they were "randomised" (Chapel 2009; Kane 2011; NCT00151424; Kane 2010; NCT00156117; Potkin 2007). Furthermore, no study provides information on allocation concealment. As a result we had to rate all studies as being of 'unclear' risk of bias.

Blinding

All the included studies described blinding as "double-blind", however four of the six provide no further detail as to how this was achieved (Chapel 2009; NCT00151424; Kane 2010; NCT00156117). For this reason, we have rated them as 'unclear risk'. Potkin 2007 and Kane 2011 we rated 'low risk' as both studies provide some description of how the blinding was conducted. A double dummy design was used where asenapine and placebo tablets were identical in appearance and the patients and sites were unaware of the identity of the tablets (Kane 2011, Potkin 2007). The authors judge Kane 2011, to be 'high risk' in the assessment of an outcome. The rest of the studies do not describe how blinding was done to assess the outcomes, therefore, they were deemed as 'unclear risk'.

Incomplete outcome data

All six included studies report loss to follow up and attrition due to adverse effects, although this is not well documented in some. Some attempt was made by five studies to address the attrition by using the intention-to-treat (ITT) approach (Kane 2011; NCT00151424; Kane 2010; NCT00156117; Potkin 2007;). However, in Kane 2011; NCT00151424; Kane 2010; Potkin 2007 , the ITT approach was used in conjunction with last observation carried forward (LOCF) for some of the outcomes. This can introduce bias as it makes assumptions about the people who did not complete the study. None of these studies attempted to validate the assumptions made about these people and because of this, we have rated them as 'high risk'. Chapel 2009 does not document how the loss of participants was addressed for analysis and this, too, has been rated as 'high risk'.

Selective reporting

Most of the studies had some degree of selective reporting or insufficient reporting of data - with the exception of Kane 2010 which we thought was 'low risk' as it provides usable data for most outcomes. NCT00151424 and NCT00156117 are unpublished trials with full data sets unavailable, however, we were able to utilise some data for mental state, leaving the study early and adverse effects. The majority of studies provided tables, graphs and visual representations of data. Some studies reported no means or standard deviations for certain outcomes (Kane 2011; Potkin 2007). Chapel 2009 had unreported data of endpoint characteristics for its primary outcome. We rated Chapel 2009; Kane 2011; NCT00151424; NCT00156117; Potkin 2007 as 'high risk' due to missing, incomplete or unusable reporting of data.

Other potential sources of bias

All six studies were funded and supported by pharmaceutical companies (Merck, Organon, Pfizer Inc, Schering-Plough). Nearly all authors were affiliated with or employed by pharmaceutical companies. This could lead to bias in the reporting. As a result, we classed all the studies at 'high risk'.

Effects of interventions

See: **Summary of findings for the main comparison** ASENAPINE versus PLACEBO for schizophrenia

COMPARISON 1: ASENAPINE versus PLACEBO

1.1 Global state: 1. No clinically important change (CGI-I) - short-term (up to 12 weeks)

For this outcome we only found one relevant trial (n = 336) (Kane 2010). There was a clear difference between asenapine and placebo (RR 0.81, 95% CI 0.68 to 0.97, Analysis 1.1).

1.2 Global state: 2. Average change score (CGI-S, high = poor)

1.2.1 Short-term (up to 12 weeks)

In this subgroup we only found one relevant trial (n = 336) (Kane 2010). There was a clear difference between asenapine and placebo (MD - 0.35, 95% CI -0.55 to -0.15, Analysis 1.2).

1.2.2 Medium-term (13 to 26 weeks)

In this subgroup we only found one relevant trial (n = 382) (Kane 2011). There was a clear difference between asenapine and placebo (MD -0.6, 95% CI -0.77 to -0.43, Analysis 1.2).

1.3 Global state: 3. Relapse - medium-term (13 to 26 weeks)

For this outcome we only found one relevant trial (n = 386) (Kane 2011). There was a clear difference between asenapine and placebo (RR 0.26, 95% CI 0.18 to 0.40, Analysis 1.3).

1.4 Global state: 4. Use of any concomitant medication

1.4.1 Short-term

In this subgroup we only found one relevant trial (n = 340) (Kane 2010). There was a clear difference between asenapine and placebo (RR 0.84, 95% CI 0.74 to 0.97, Analysis 1.4).

1.4.2 Medium-term

In this subgroup we only found one relevant trial (n = 386) (Kane 2011). There was no clear difference between asenapine and placebo (RR 0.87, 95% CI 0.71 to 1.07, Analysis 1.4).

1.5 Global state: 5. Use of specific concomitant medication

1.5.1 Acetaminophen - short-term

In this subgroup we only found one relevant trial (n = 340) (Kane 2010). There was no clear difference between asenapine and placebo (RR 0.74, 95% CI 0.48 to 1.12, Analysis 1.5).

1.5.2 Antiparkinsonian medication - short-term

In this subgroup we found two relevant trials (n = 461). There was no clear difference between asenapine and placebo (RR 1.21, 95% CI 0.78 to 1.88, Analysis 1.5). This subgroup had moderate levels of heterogeneity (Chi^2 = 1.62; degrees of freedom (df) = 1; P = 0.203; I^2 = 38%).

1.5.3 Benzatropine - short-term

In this subgroup we only found one relevant trial (n = 340) (Kane 2010). There was no clear difference between asenapine and placebo (RR 1.05, 95% CI 0.43 to 2.57, Analysis 1.5).

1.5.4 Ibuprofen - short-term

In this subgroup we only found one relevant trial (n = 340) (Kane 2010). There was no clear difference between asenapine and placebo (RR 0.61, 95% CI 0.30 to 1.22, Analysis 1.5).

1.5.5 Lorazepam - short-term

In this subgroup we found two relevant trials (n = 461). There was no clear difference between asenapine and placebo (RR 0.85, 95% CI 0.71 to 1.02, Analysis 1.5).

1.5.6 Lorazepam - medium-term

In this subgroup we only found one relevant trial (n = 386) (Kane 2011). There was no clear difference between asenapine and placebo (RR 0.45, 95% CI 0.16 to 1.27, Analysis 1.5).

1.5.7 Trihexyphenidyl - short-term

In this subgroup we only found one relevant trial (n = 340) (Kane 2010). There was no clear difference between asenapine and placebo (RR 1.70, 95% CI 0.83 to 3.50, Analysis 1.5).

1.5.8 Trihexyphenidyl - medium-term

In this subgroup we only found one relevant trial (n = 386) (Kane 2011). There was no clear difference between asenapine and placebo (RR 0.66, 95% CI 0.19 to 2.30, Analysis 1.5).

1.5.9 Zolpidem - short-term

In this subgroup we found two relevant trials (n = 461). There was no clear difference between asenapine and placebo (RR 1.00, 95% CI 0.71 to 1.40, Analysis 1.5).

1.5.10 Zolpidem - medium-term

In this subgroup we only found one relevant trial (n = 386) (Kane 2011). There was no clear difference between asenapine and placebo (RR 0.33, 95% CI 0.07 to 1.61, Analysis 1.5).

1.6 Mental state: 1. No clinically important change (PANSS) - short-term

For this outcome we only found one relevant trial (n = 336) (Kane 2010). There was a clear difference between asenapine and placebo (RR 0.72, 95% CI 0.59 to 0.86, Analysis 1.6).

1.7 Mental state: 2. Average change in total score (baseline-to-endpoint) (PANSS, high = poor)

1.7.1 PANSS total score - short-term

In this subgroup we found two relevant trials (n = 627). There was a clear difference between asenapine and placebo (MD -3.77, 95% CI -6.50 to -1.04, Analysis 1.7).

1.7.2 PANSS total score - medium-term

In this subgroup we only found one relevant trial (n = 382) (Kane 2011). There was a clear difference between asenapine and placebo (MD -10.80, 95% CI -13.57 to -8.03, Analysis 1.7).

1.8 Mental state: 3. Average change score (baseline-to-endpoint) (various scales, high = poor)

1.8.1 CDSS total score - short-term

In this subgroup we only found one relevant trial (n = 336) (Kane 2010). There was a clear difference between asenapine and placebo (MD -0.86, 95% CI -1.62 to -0.10, Analysis 1.8).

1.8.2 CDSS total score - medium-term

In this subgroup we only found one relevant trial (n = 382) (Kane 2011). There was a clear difference between asenapine and placebo (MD -0.70, 95% CI -1.25 to -0.15, Analysis 1.8).

1.8.3 PANSS Marder anxiety/depression factor score - short-term

In this subgroup we only found one relevant trial (n = 336) (Kane 2010). There was a clear difference between asenapine and placebo (MD -0.55, 95% CI -1.26 to 0.16, Analysis 1.8).

1.8.4 PANSS Marder anxiety/depression factor score - medium-term

In this subgroup we only found one relevant trial (n = 382) (Kane 2011). There was a clear difference between asenapine and placebo ((MD -1.40, 95% CI -1.95 to -0.85), Analysis 1.8).

1.8.5 PANSS Marder disorganized thought factor score - short-term

In this subgroup we only found one relevant trial (n = 336) (Kane 2010). There was a clear difference between asenapine and placebo (MD -1.25, 95% CI -2.20 to -0.30, Analysis 1.8).

1.8.6 PANSS Marder disorganized thought factor score - medium-term

In this subgroup we only found one relevant trial (n = 382) (Kane 2011). There was a clear difference between asenapine and placebo (MD -2.40, 95% CI -2.95 to -1.85, Analysis 1.8).

1.8.7 PANSS Marder hostility/excitement factor score - short-term

In this subgroup we only found one relevant trial (n = 336) (Kane 2010). There was a clear difference between asenapine and placebo (MD -0.50, 95% CI -1.21 to 0.21, Analysis 1.8).

1.8.8 PANSS Marder hostility/excitement factor score - medium-term

In this subgroup we only found one relevant trial (n = 382) (Kane 2011). There was a clear difference between asenapine and placebo (MD -2.00, 95% CI -2.55 to -1.45, Analysis 1.8).

1.8.9 PANSS Marder negative factor score - short-term

In this subgroup we only found one relevant trial (n = 336) (Kane 2010). There was a clear difference between asenapine and placebo (MD -1.10, 95% CI -2.29 to 0.09, Analysis 1.8).

1.8.10 PANSS Marder negative factor score - medium-term

In this subgroup we only found one relevant trial (n = 382) (Kane 2011). There was a clear difference between asenapine and placebo (MD -1.70, 95% CI -2.53 to -0.87, Analysis 1.8).

1.8.11 PANSS Marder positive factor score - short-term

In this subgroup we only found one relevant trial (n = 336) (Kane 2010). There was a clear difference between asenapine and placebo (MD -2.40, 95% CI -3.83 to -0.97, Analysis 1.8).

1.8.12 PANSS Marder positive factor score - medium-term

In this subgroup we only found one relevant trial (n = 382) (Kane 2011). There was a clear difference between asenapine and placebo (MD -3.40, 95% CI -4.23 to -2.57, Analysis 1.8).

1.9 Adverse effects: 1. Incidence of serious adverse effects

1.9.1 Short-term

In this subgroup we found three relevant trials (n = 644). There was no clear difference between asenapine and placebo (RR 1.12, 95% CI 0.63 to 2.00, Analysis 1.9).

1.9.2 Medium-term

In this subgroup we only found one relevant trial (n = 386) (Kane 2011). There was a clear difference between asenapine and placebo (RR 0.29, 95% CI 0.14 to 0.63, Analysis 1.9).

1.10 Adverse effects: 2. Incidence of any adverse effects

1.10.1 Any adverse effects - short-term

In this subgroup we found two relevant trials (n = 461). There was no clear difference between asenapine and placebo (RR 0.99, 95% CI 0.89 to 1.11, Analysis 1.10).

1.10.2 Any treatment-emergent adverse effects - medium-term

In this subgroup we only found one relevant trial (n = 386) (Kane 2011). There was no clear difference between asenapine and placebo (RR 0.83, 95% CI 0.68 to 1.01, Analysis 1.10).

1.10.3 Any treatment-related adverse effects - short-term

In this subgroup we only found one relevant trial (n = 340) (Kane 2010). There was no clear difference between asenapine and placebo (RR 1.18, 95% CI 0.91 to 1.52, Analysis 1.10).

1.10.4 Any treatment-related adverse effects - medium-term

In this subgroup we only found one relevant trial (n = 386) (Kane 2011). There was no clear difference between asenapine and placebo (RR 0.84, 95% CI 0.59 to 1.19, Analysis 1.10).

1.11 Adverse effects: 3. Incidence of adverse effects by severity - short-term

1.11.1 Mild adverse effects

In this subgroup we only found one relevant trial (n = 340) (Kane 2010). There was no clear difference between asenapine and placebo (RR 0.88, 95% CI 0.66 to 1.18, Analysis 1.11).

1.11.2 Moderate adverse effects

In this subgroup we only found one relevant trial (n = 340) (Kane 2010). There was no clear difference between asenapine and placebo (RR 1.01, 95% CI 0.71 to 1.42, Analysis 1.11).

1.11.3 Severe adverse effects

In this subgroup we found three relevant trials (n = 644). There was no clear difference between asenapine and placebo (RR 1.52, 95% CI 0.80 to 2.91, Analysis 1.11).

1.12 Adverse effects: 4. Specific adverse effects - 4.1. Cardiovascular: incidence - short-term

1.12.1 QTc interval > 450 ms

In this subgroup we found two relevant trials (n = 232). There was a clear difference between asenapine and placebo (RD - 0.01, 95% CI - 0.07 to 0.05, Analysis 1.12).

1.12.2 Sinus tachycardia

In this subgroup we only found one relevant trial (n = 121) (Potkin 2007). There was a clear difference between asenapine and placebo (RD 0.01, 95% CI -0.11 to 0.12, Analysis 1.12).

1.13 Adverse effects: 4. Specific adverse effects - 4.2. Gastrointestinal: incidence - short-term

1.13.1 Clinically significant gamma-glutamyl transpeptidase levels

In this subgroup we only found one relevant trial (n = 183) (NCT00151424). There was a clear difference between asenapine and placebo (RR 3.62, 95% CI 1.24 to 10.57, Analysis 1.13).

1.13.2 Clinically significant alanine aminotransferase levels

In this subgroup we only found one relevant trial (n = 183) (NCT00151424). There was a clear difference between asenapine and placebo (RR 2.58, 95% CI 1.2 to 5.56, Analysis 1.13).

1.13.3 Constipation

In this subgroup we only found one relevant trial (n = 121) (Potkin 2007). There was no clear difference between asenapine and placebo (RR 1.05, 95% CI 0.36 to 3.08, Analysis 1.13).

1.13.4 Dyspepsia

In this subgroup we only found one relevant trial (n = 121) (Potkin 2007). There was no clear difference between asenapine and placebo (RR 0.84, 95% CI 0.24 to 2.98, Analysis 1.13).

1.13.5 Vomiting

In this subgroup we found two relevant trials (n = 461). There was no clear difference between asenapine and placebo (RR 1.31, 95% CI 0.61 to 2.84, Analysis 1.13).

1.14 Adverse effects: 4. Specific adverse effects - 4.3. Metabolic: incidence

1.14.1 Clinically significant fasting glucose levels - short-term

In this subgroup we found three relevant trials (n = 641). There was a clear difference between asenapine and placebo (RR 2.24, 95% CI 1.06 to 4.75, Analysis 1.14). This subgroup had moderate levels of heterogeneity (Chi^2 = 3.97; df = 2; P = 0.14; I^2 = 50%).

1.14.2 Clinically significant fasting triglycerides levels - short-term

In this subgroup we only found one relevant trial (n = 183) (NCT00151424). There was a clear difference between asenapine and placebo (RR 8.27, 95% CI 1.06 to 64.77, Analysis 1.14).

1.14.3 Clinically significant HbA1C levels - short-term

In this subgroup we only found one relevant trial (n = 183) (NCT00151424). There was no clear difference between asenapine and placebo (RR 7.23, 95% CI 0.38 to 138.03, Analysis 1.14).

1.14.4 Clinically significant hyperprolactinaemia - short-term

In this subgroup we found two relevant trials (n = 458). There was no clear difference between asenapine and placebo (RR 3.28, 95% CI 0.97 to 11.06, Analysis 1.14).

1.14.5 Clinically significant hyperprolactinaemia - medium-term

In this subgroup we only found one relevant trial (n = 386) (Kane 2011). There was no clear difference between asenapine and placebo (RR 0.62, 95% CI 0.21 to 1.86, Analysis 1.14).

1.14.6 Clinically significant weight gain - short-term

In this subgroup we found three relevant trials (n = 623). There was a clear difference between asenapine and placebo (RR 3.48, 95% CI 1.19 to 10.15, Analysis 1.14).

1.14.7 Clinically significant weight gain - medium-term

In this subgroup we only found one relevant trial (n = 386) (Kane 2011). There was no clear difference between asenapine and placebo (RR 6.93, 95% CI 0.86 to 55.77, Analysis 1.14).

1.14.8 Clinically significant weight loss - short-term

In this subgroup we only found one relevant trial (n = 340) (Kane 2010). There was no clear difference between asenapine and placebo (RR 0.85 CI 0.14 to 5.02, Analysis 1.14).

1.14.9 Clinically significant weight loss - medium-term

In this subgroup we only found one relevant trial (n = 386) (Kane 2011). There was a clear difference between asenapine and placebo (RR 0.33, 95% CI 0.13 to 0.81, Analysis 1.14).

1.14.10 Weight gain - medium-term

In this subgroup we only found one relevant trial (n = 386) (Kane 2011). There was no clear difference between asenapine and placebo (RR 1.84, 95% CI 0.75 to 4.51, Analysis 1.14).

1.14.11 Weight loss - medium-term

In this subgroup we only found one relevant trial (n = 386) (Kane 2011). There was no clear difference between asenapine and placebo (RR 0.43 , 95%CI 0.18 to 1.03, Analysis 1.14).

1.15 Adverse effects: 4. Specific adverse effects - 4.4. Metabolic: average change in prolactin levels (μg/L) (baseline-to-endpoint) - short-term

For this outcome we only found one relevant trial (n = 340) (Kane 2010). There was no clear difference between asenapine and placebo (MD 6.01, 95% CI - 3.35 to 15.37, Analysis 1.15).

1.16 Adverse effects: 4. Specific adverse effects - 4.5. Metabolic: average change in weight (kg) (baseline-to-endpoint)

1.16.1 Short-term

In this subgroup we only found one relevant trial (n = 340) (Kane 2010). There was no clear difference between asenapine and placebo (MD 1.05, 95% CI -0.03 to 2.13, Analysis 1.16).

1.16.2 Medium-term

In this subgroup we only found one relevant trial (n = 386) (Kane 2011). There was no clear difference between asenapine and placebo (MD 1.20, 95% CI 0.46 to 1.94, Analysis 1.16).

1.17 Adverse effects: 4. Specific adverse effects - 4.6. Other specific adverse effects: incidence

1.17.1 Agitation - short-term

In this subgroup we found two relevant trials (n = 461). There was a clear difference between asenapine and placebo (RR 0.50, 95% CI 0.28 to 0.89, Analysis 1.17).

1.17.2 Agitation - medium-term

In this subgroup we only found one relevant trial (n = 386) (Kane 2011). There was no clear difference between asenapine and placebo (RR 0.36, 95% CI 0.12 to 1.11, Analysis 1.17).

1.17.3 Akathisia - short-term

In this subgroup we only found one relevant trial (n = 340) (Kane 2010). There was no clear difference between asenapine and placebo (RR 1.84, 95% CI 0.61 to 5.53, Analysis 1.17).

1.17.4 Akathisia - medium-term

In this subgroup we only found one relevant trial (n = 386) (Kane 2011). There was no clear difference between asenapine and placebo (RR 1.32, 95% CI 0.3 to 5.82, Analysis 1.17).

1.17.5 Anxiety - short-term

In this subgroup we found two relevant trials (n = 461). There was no clear difference between asenapine and placebo (RR 1.01, 95% CI 0.52 to 1.96, Analysis 1.17).

1.17.6 Anxiety - medium-term

In this subgroup we only found one relevant trial (n = 386) (Kane 2011). There was no clear difference between asenapine and placebo (RR 0.75, 95% CI 0.41 to 1.40, Analysis 1.17).

1.17.7 Delusions - medium-term

In this subgroup we only found one relevant trial (n = 386) (Kane 2011). There was a clear difference between asenapine and placebo (RR 0.18, 95% CI 0.04 to 0.80, Analysis 1.17).

1.17.8 Dizziness - short-term

In this subgroup we only found one relevant trial (n = 121) (Potkin 2007). There was no clear difference between asenapine and placebo (RR 0.58, 95% CI 0.21 to 1.64, Analysis 1.17).

1.17.9 Fatigue - short-term

In this subgroup we only found one relevant trial (n = 121) (Potkin 2007). There was no clear difference between asenapine and placebo (RR 0.53, 95% CI 0.10 to 2.76, Analysis 1.17).

1.17.10 Hallucinations - medium-term

In this subgroup we only found one relevant trial (n = 386) (Kane 2011). There was a clear difference between asenapine and placebo (RR 0.08, 95% CI 0.01 to 0.58, Analysis 1.17).

1.17.11 Headache - short-term

In this subgroup we found two relevant trials (n = 461). There was a clear difference between asenapine and placebo (RR 0.39, 95% CI 0.22 to 0.71, Analysis 1.17).

1.17.12 Headache - medium-term

In this subgroup we only found one relevant trial (n = 386) (Kane 2011). There was no clear difference between asenapine and placebo (RR 2.97, 95% CI 0.61 to 14.53, Analysis 1.17).

1.17.13 Insomnia - short-term

In this subgroup we found two relevant trials (n = 461). There was no clear difference between asenapine and placebo (RR 0.81, 95% CI 0.50 to 1.31, Analysis 1.17). This subgroup had important levels of heterogeneity (Chi^2 = 2.79; df = 1; P = 0.09; I^2 = 64%).

1.17.14 Insomnia - medium-term

In this subgroup we only found one relevant trial (n = 386) (Kane 2011). There was a clear difference between asenapine and placebo (RR 0.46, 95% CI 0.24 to 0.88, Analysis 1.17).

1.17.15 Nausea - short-term

In this subgroup we only found one relevant trial (n = 121) (Potkin 2007). There was no clear difference between asenapine and placebo (RR 1.44, 95% CI 0.62 to 3.34, Analysis 1.17).

1.17.16 Oral hypoesthesia - short-term

In this subgroup we only found one relevant trial (n = 340) (Kane 2010). There was no clear difference between asenapine and placebo (RR 1.89, 95% CI 0.53 to 6.74, Analysis 1.17).

1.17.17 Pain - short-term

In this subgroup we only found one relevant trial (n = 121) (Potkin 2007). There was no clear difference between asenapine and placebo (RR 0.79, 95% CI 0.18 to 3.37, Analysis 1.17).

1.17.18 Psychosis - short-term

In this subgroup we only found one relevant trial (n = 121) (Potkin 2007). There was no clear difference between asenapine and placebo (RR 1.58, 95% CI 0.47 to 5.31, Analysis 1.17).

1.17.19 Schizophrenia - medium-term

In this subgroup we only found one relevant trial (n = 386) (Kane 2011). There was a clear difference between asenapine and placebo (RR 0.29, 95% CI 0.14 to 0.59, Analysis 1.17).

1.17.20 Sedation - short-term

In this subgroup we only found one relevant trial (n = 340) (Kane 2010). There was no clear difference between asenapine and placebo (RR 0.68, 95% CI 0.21 to 2.18, Analysis 1.17).

1.17.21 Somnolence - short-term

In this subgroup we found two relevant trials (n = 461). There was no clear difference between asenapine and placebo (RR 1.88, 95% CI 0.86 to 4.08, Analysis 1.17).

1.17.22 Somnolence - medium-term

In this subgroup we only found one relevant trial (n = 386) (Kane 2011). There was no clear difference between asenapine and placebo (RR 0.49, 95% CI 0.05 to 5.41, Analysis 1.17).

1.17.23 Upper respiratory tract infection - short-term

In this subgroup we only found one relevant trial (n = 121) (Potkin 2007). There was no clear difference between asenapine and placebo (RR 1.4, 95% CI 0.33 to 6.00, Analysis 1.17).

1.17.24 Worsening psychotic symptoms - short-term

In this subgroup we only found one relevant trial (n = 340) (Kane 2010). There was no clear difference between asenapine and placebo (RR 0.51, 95% CI 0.21 to 1.22, Analysis 1.17).

1.18 Adverse effects: 5. Extrapyramidal symptoms - 5.1. Incidence

1.18.1 Any extrapyramidal symptoms - short-term

In this subgroup we found two relevant trials (n = 523). There was a clear difference between asenapine and placebo (RR 1.74, 95% CI 1.02 to 2.96, Analysis 1.18).

1.18.2 Any extrapyramidal symptoms - medium-term

In this subgroup we only found one relevant trial (n = 386) (Kane 2011). There was no clear difference between asenapine and placebo (RR 0.66, 95% CI 0.24 to 1.82, Analysis 1.18).

1.18.3 Dystonia - short-term

In this subgroup we only found one relevant trial (n = 340) (Kane 2010). There was no clear difference between asenapine and placebo (RR 7.39, 95% CI 0.42 to 130.15, Analysis 1.18).

1.18.4 Hyperkinesia - short-term

In this subgroup we only found one relevant trial (n = 121) (Potkin 2007). No one experienced this outcome (Analysis 1.18).

1.18.5 Hypertonia - short-term

In this subgroup we only found one relevant trial (n = 121) (Potkin 2007). There was no clear difference between asenapine and placebo (RR 0.21, 95% CI 0.01 to 4.28, Analysis 1.18).

1.18.6 Muscle rigidity - short-term

In this subgroup we only found one relevant trial (n = 340) (Kane 2010). There was no clear difference between asenapine and placebo (RR 8.53, 95% CI 0.49 to 148.12, Analysis 1.18).

1.18.7 Parkinsonism - short-term

In this subgroup we only found one relevant trial (n = 340) (Kane 2010). There was no clear difference between asenapine and placebo (RR 1.51, 95% CI 0.61 to 3.76, Analysis 1.18).

1.18.8 Parkinsonism - medium-term

In this subgroup we only found one relevant trial (n = 386) (Kane 2011). There was no clear difference between asenapine and placebo (RR 0.33, 95% CI 0.03 to 3.14, Analysis 1.18).

1.19 Adverse effects: 5. Extrapyramidal symptoms - 5.2. Average change (baseline-to-endpoint) (various scales, high = poor) - short-term

1.19.1 AIMS

In this subgroup we only found one relevant trial (n = 333) (Kane 2010). There was a clear difference between asenapine and placebo (MD -0.13, 95% CI -0.43 to 0.17, Analysis 1.19).

1.19.2 BAS

In this subgroup we only found one relevant trial (n = 333) (Kane 2010). There was a clear difference between asenapine and placebo (MD 0.11, 95% CI -0.05 to 0.27, Analysis 1.19).

1.19.3 SAS

In this subgroup we only found one relevant trial (n = 333) (Kane 2010). There was no clear difference between asenapine and placebo (MD 0.50, 95% CI -0.04 to 1.04, Analysis 1.19).

1.20 Adverse effects: 6. Incidence of death (for any reason) - short-term

In this outcome we found two relevant trials (n = 523). There was no clear difference between asenapine and placebo (RD -0.01, 95% CI -0.02 to 0.01, Analysis 1.20).

1.21 Leaving the study early

1.21.1 Any reason - short-term

In this subgroup we found five relevant trials (n = 1046). There was no clear difference between asenapine and placebo (RR 0.91, 95% CI 0.80 to 1.04, Analysis 1.21). This subgroup had moderate levels of heterogeneity (Chi^2 = 7.02; df = 4; P = 0.13; I^2 = 43%).

1.21.2 Any reason - medium-term

In this subgroup we only found one relevant trial (n = 386) (Kane 2011). There was a clear difference between asenapine and placebo (RR 0.49, 95% CI 0.38 to 0.62, Analysis 1.21).

1.21.3 Due to adverse effects - short-term

In this subgroup we found three relevant trials (n = 644). There was no clear difference between asenapine and placebo (RR 0.89, 95% CI 0.54 to 1.47, Analysis 1.21).

1.21.4 Due to adverse effects - medium-term

In this subgroup we only found one relevant trial (n = 386) (Kane 2011). There was a clear difference between asenapine and placebo (RR 0.3, 95% CI 0.18 to 0.50, Analysis 1.21).

1.21.5 Due to lack of efficacy - short-term

In this subgroup we found two relevant trials (n = 457). There was a clear difference between asenapine and placebo (RR 0.56, 95% CI 0.38 to 0.81, Analysis 1.21).

1.21.6 Due to loss to follow up - medium-term

In this subgroup we only found one relevant trial (n=386) (Kane 2011). There was not a clear difference between asenapine and placebo (RR 0.99 CI 0.2 to 4.84, Analysis 1.21).

1.21.7 Due to other reasons - short-term

In this subgroup we found two relevant trials (n = 457). There was no clear difference between asenapine and placebo (RR 1.22, 95% CI 0.83 to 1.80, Analysis 1.21).

1.21.8 Due to other reasons - medium-term

In this subgroup we only found one relevant trial (n = 386) (Kane 2011). There was no clear difference between asenapine and placebo (RR 0.84, 95% CI 0.38 to 1.82, Analysis 1.21).

1.21.9 Due to relapse (not considered adverse effect) - medium-term

In this subgroup we only found one relevant trial (n = 386) (Kane 2011). There was a clear difference between asenapine and placebo (RR 0.25, 95% CI 0.13 to 0.49, Analysis 1.21).

1.21.10 Due to specific adverse effect: relapse - medium-term

In this subgroup we only found one relevant trial (n = 386) (Kane 2011). There was a clear difference between asenapine and placebo (RR 0.27 CI, 95% 0.16 to 0.47, Analysis 1.21).

1.21.11 Due to specific adverse effect: worsening of schizophrenia - medium-term

In this subgroup we only found one relevant trial (n = 386) (Kane 2011). There was a clear difference between asenapine and placebo (RR 0.25, 95% CI 0.14 to 0.45, Analysis 1.21).

1.21.12 Due to withdrawal of consent - medium-term

In this subgroup we only found one relevant trial (n = 386) (Kane 2011). There was no clear difference between asenapine and placebo (RR 1.57, 95% CI 0.78 to 3.14, Analysis 1.21).

2. Subgroup analyses

No subgroup analyses were conducted.

3. Sensitivity analyses

3.1 Implication of randomisation

No sensitivity analyses were possible, as all included studies for the primary outcomes were explicitly described as having random allocation procedures.

3.2 Assumptions for lost binary data

For the primary outcomes, no sensitivity analyses were possible, as no included study reported binary data for completer-only populations.

3.3 Risk of bias

No sensitivity analyses were possible, as all included studies for the primary outcomes were judged to be of high risk of bias in one or more domains (randomisation, allocation concealment, blinding and outcome reporting).

3.4 Imputed values

No sensitivity analyses were possible, as none of the included studies for the primary outcomes were cluster-randomised trials.

3.5 Fixed and random effects

For the primary outcomes, there was no difference in the results when synthesising data using a fixed-effect model or a random-effects model.

DISCUSSION

Summary of main results

1. General

Six studies (29 reports) met the inclusion criteria for our review. The summary below discusses the outcomes included in Summary of findings for the main comparison. We have also considered the impact of our findings upon clinical practice, patients' decision-making and policy-related directives.

2. Treatment effects

2.1 Clinically important change in global state

One short-term study (Kane 2010; n = 336) reported the outcome of clinically important change in global state (considered by this study as a CGI-I score of one or two). Compared with placebo, asenapine was found to produce significantly greater clinical change in global state. Although encouraging, this finding must be considered with caution because of the 'low-quality' and limited quantity of evidence.

2.2 Clinically important change in mental state

The same short-term study (Kane 2010; n = 336) reported 'clinically important change in mental state' (considered as a > 30% decrease in PANSS score). Compared with placebo, asenapine was found to produce significantly greater clinical change in mental state. Again, interpretation must be undertaken with caution because of the 'very low-quality' and limited quantity of evidence.

2.3 Average change in negative symptoms

Again, the same short-term study (Kane 2010; n = 336) reported on the outcome of average change in negative symptoms (measured in this study using the PANSS Marder negative factor). Compared with placebo, asenapine was found to produce significantly greater reduction in negative symptoms. Again, caution must be taken when interpreting this result due to the 'very low-quality' and limited quantity of evidence. This needs much more independent verification.

2.4 Incidence of serious adverse effects

One medium-term study (Kane 2011; n=386) reported on the outcome of incidence of serious adverse effects. Compared with placebo, asenapine was found to produce significantly fewer incidents of serious adverse effects. Again, caution must be taken when interpreting this result due to the 'very low-quality' and limited quantity of evidence. Additionally, Analysis 1.9 shows three short-term studies also indicate no differences between asenapine and placebo in the incidence of serious adverse effects. One would expect an active drug to have adverse effects and some of these, perhaps occasionally, to be serious. It could be that asenapine is not associated with adverse effects that are serious. It could also be that more trial-derived data are needed, as well as information from other non-trial sources. It is also feasible that, in these trials, selective reporting is more than a possibility. More independently-derived data are needed.

2.5 Clinically significant extrapyramidal symptoms

Although four studies reported on incidence of extrapyramidal symptoms, and two reported on average change of extrapyramidal symptoms from baseline-to-endpoint (using the AIMS, BAS and SAS), no included trial reported on the incidence of clinically significant extrapyramidal symptoms. Continuous measures are important fine-grain ways of identifying symptoms or signs. However, it adds little complexity to a study to ask raters or participants about how important they really feel that problem to be. Not to do this could impose a spurious importance to data, or serve to help ignore issues that really bother people. This omission is an indication that these studies were designed less for research into the well being of people with schizophrenia and more for the needs of companies.

2.6 Leaving the study early - for any reason

Five short-term studies (n = 1046) reported on the outcome of 'leaving the study early for any reason'. Analysis 1.21 indicates that there is no difference between the discontinuation rates of asenapine and placebo across the studies. While this may appear encouraging for the use of asenapine, discontinuation rates for asenapine (42.5%) and placebo (48.7%) were both very high. Although our analysis was characterised by moderate heterogeneity (I^2 = 43%), and differences in discontinuation became clear, favouring asenapine, when the one outlying study Chapel 2009 (~2% weighting) is removed to gain homogeneity, losses to follow up are still enormous. While four studies attempt to report on specific reasons for discontinuation, the similarly high rates of attrition are likely to reflect poor study design and trial management. The most chaotic of clinical situations would still be hard pressed to lose nearly half the people with schizophrenia it was responsible for within a matter of six weeks. This indicates how odd and removed from real world care these trials are.

2.7 Economic costs

We considered the direct and indirect economic costs of asenapine treatment to be a highly important outcome that could influence its potential circulation in clinical practice for schizophrenia. Suprisingly, no studies reported any data related to this outcome. No study reported service use outcomes such as 'relapse' or 'hospitalisation'. These can often be used as a proxy in an economic consideration of an intervention. With economics being such an important part of consideration of care, it is notable that there are no data at all for this new compound. It is hard not to conclude that the companies producing these trials are hesitant about reporting any data which would lead to economic consideration.

3. Publication bias

Due to the limited number of studies, it was not sensible to conduct funnel plot analyses to investigate publication bias. However we were unable to find full publications for two included studies (NCT00151424; NCT00156117) that were considered to be 'negative trials' by their authors.

4. Subgroup analyses

We did not conduct subgroup analyses.

5. Sensitivity analyses

No sensitivity analyses were possible for the implication of randomisation, assumptions for lost binary data, risk of bias, and imputed values. The results for the primary outcomes did not differ when a random-effects model was applied instead of a fixed-effect model.

Overall completeness and applicability of evidence

1. Completeness

1.1 Outcomes

The outcomes that were reported by the studies that have been included are global state, mental state, adverse effects and leaving the study early.

For the primary outcomes, only Kane 2010 reported on clinically important change in global state and clinically important change in mental state. Therefore we consider that our included studies insufficiently reported these primary outcomes.

Similarly, our included studies inconsistently reported on the majority of our secondary outcomes. Of our analyses, only the outcome 'leaving the study early' (Analysis 1.21) was reported on by all six of our included studies.

None of the included studies had any evidence of the effects of asenapine versus placebo on cognitive functioning, behaviour, functioning, service utilisation, quality of life, and economic costs. Of the secondary outcomes, we believe the insufficient reporting of 'relapse', and not reporting service outcomes such as 'admitted', particularly disappointing.

1.2 Duration

Of our included studies, five were short-term and one was medium-term. We found no long-term studies.

2. Applicability

2.1 Patients

Four of our included studies were global multicentred trials which indicates the applicability of asenapine across different cultures. However no included study reported a breakdown of participant sample size and demographics of each centre from which we could draw stronger conclusions.

The majority of included studies predominately consisted of patients with schizophrenia (DSM-IV/DSM-IV-TR) which limits the applicability of our findings to other schizophrenia-like disorders (e.g. schizo-affective disorder, schizophreniform disorder, delusional disorder). Furthermore, no included study clearly reported upon the presence of psychiatric and physical co-morbidities. In addition, several included studies explicitly excluded co-morbid conditions, which does not reflect everyday clinical practice. Therefore it is unclear whether our findings are applicable to co-morbid populations.

2.2 Dosage

The dose of asenapine ranged from 5 mg to 20 mg twice a day (BID). The dosage used by five of the included studies adhered to the FDA recommendations (5 - 10 mg BID) (FDA 2013), suggesting clinical applicability of the findings. Only one study (Chapel 2009) exceeded the recommended dosage, using up to 20 mg BID.

2.3 Setting

Three included studies conducted the trial on an inpatient and outpatient basis. However no study reported a breakdown of outcome findings from each setting type. The settings of the other included studies have not been clearly specified. In this respect, the applicability of the findings is unclear.

2.4 Outcome term lengths

Five of our included studies were short-term and one was medium-term. We found no long-term studies. Considering schizophrenia is a chronic illness and may require long-term medication treatment, we consider the applicability of the short-term studies to be limited, as far as the long-term prognosis of patients with schizophrenia is concerned.

Quality of the evidence

We judged the bias of the included trials to be unclear/high (Figure 3; Figure 4), and the quality of the current evidence to be low or very low using GRADE (Summary of findings for the main comparison) (Schünemann 2011). This is largely due to poor trial design and management, methodological inadequacies (randomisation and blinding), and high rates of discontinuation. In addition, the included studies were characterised by missing or unreported outcomes and poor clarity of follow-up. All trials were sponsored by pharmaceutical companies and nearly all authors were affiliated with, or employed by these companies.

Potential biases in the review process

We adhered to the protocol by independently inspecting citations and full articles of potentially relevant studies. Furthermore we independently extracted data onto simple forms, and discussed any inconsistencies or disagreements that arose.

Agreements and disagreements with other studies or reviews

To our knowledge, there are no other systematic reviews of asenapine versus placebo for schizophrenia. However, a small number of pooled analyses and literature reviews (Bishara 2009; Citrome 2009; Leucht 2014; Stoner 2012; Szegedi 2012) were in line with the findings from our review, as many of the studies they reported were included in our analyses.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with schizophrenia

Asenapine appears to be a promising atypical antipsychotic. There is some, albeit preliminary, evidence of improvement in positive symptoms (delusions and hallucinations), negative symptoms (which may include reduced affect, and reduced motivation), and depressive symptoms. However due to the limited quality and quantity of evidence, it remains difficult to recommend the use of asenapine for schizophrenia. There are missing trials which may add to the argument about which the study authors have not been forthcoming.

2. For clinicians

The dosage used by five of the included studies adhered to the FDA recommendations (5 - 10 mg BID) (FDA 2013), suggesting clinical applicability of the findings. At present it is not possible to be fully confident that asenapine is really suitable for the treatment of people with schizophrenia, as ongoing trials are not complete or data are missing from important studies that are completed. It is

certainly impossible to make conclusive judgements on the long-term effects of asenapine.

3. For managers/policy makers

The availability of asenapine is still relatively limited. We have no real service data or economics to work with. For such a drug to enter clinical practice, we suggest that such information should be routinely produced as part of the output of evaluative studies.

Implications for research

1. General

Future studies investigating the clinical effects of asenapine need to be well reported, and adhere to the CONSORT statement (Moher 2010). All outcomes from all trials must be easily accessible and all data should be reported as numbers.

2. Specific

2.1 Reviews

This review will require updates in the future as, at present, there are two studies awaiting classification, and one ongoing trial.
Five of our included studies involved an additional active treatment arm. As detailed elsewhere, these data were excluded from this review but could be used elsewhere (Table 1). However it is important to identify the comparative effects of asenapine to other antipsychotic agents. There are two Cochrane Systematic Reviews currently underway comparing asenapine to typical antipsychotics (Kumar 2012) and other atypical antipsychotics Preda 2010).

2.2 Trials

We identify a great need for larger-scale, longer-term and more independent randomised controlled trials investigating the clinical effects and safety of asenapine. Future long-term clinical trials should clearly describe the random sequence generation and concealment of allocation, as well as the thoroughly-tested double-blinding procedures, whilst recruiting a sample size that provides high statistical power. Outcome measures that should additionally be investigated include relapse, functioning, service utilisation, quality of life/satisfaction with care, and economic costs. There are, however, studies underway or completed that may add enough to this review to allow more firm conclusions to be drawn (NCT00156091; NCT01098110; NCT01617187).

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The Cochrane Schizophrenia Group Editorial Base in Nottingham produces and maintains standard text for use in the Methods section of their reviews. We have used this text as the basis of what appears here and adapted it as required.

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REFERENCES

References to studies included in this review

Chapel 2009 *{published data only}*

* Chapel S, Hutmacher MM, Haig G, Bockbrader H, De Greef R, Preskorn SH, et al. Exposure-response analysis in patients with schizophrenia to assess the effect of asenapine on QTc prolongation. *Journal of Clinical Pharmacology* 2009;**49**(11):1297–308.

Preskorn AS, Chapel S, Panagides J. Effect of asenapine versus quetiapine and placebo on QTc interval in patients with schizophrenia. *European Neuropsychopharmacology* 2007;**17**(Suppl 4):S453.

Preskorn SH, Chapel S, Panagides J. Effects of asenapine versus placebo on QTc interval in patients with schizophrenia. American Psychiatric Association, 161st Annual Meeting, May 3-8, 2008, Washington, DC. 2008.

Kane 2010 *{published data only}*

Citrome L. Asenapine for schizophrenia and bipolar disorder: a review of the efficacy and safety profile for this newly approved sublingually absorbed second-generation antipsychotic. *The International Journal of Clinical Practice* 2009;**63**:1762–84.

Kane J, Zhao J, Cohen M, Panagides J. Efficacy and safety of asenapine in patients with acute exacerbation of schizophrenia. *Schizophrenia Research* 2008;**98**:14.

* Kane JM, Cohen M, Zhao J, Alphs L, Panagides J. Efficacy and safety of asenapine in a placebo- and haloperidol-controlled trial in patients with acute exacerbation of schizophrenia. *Journal of Clinical Psychopharmacology* 2010; **30**(2):106–15.

Kane JM, Zhao J, Cohen M, Panagides J. Efficacy and safety of asenapine in patients with acute schizophrenia. American Psychiatric Association, 161st Annual Meeting, May 3-8, 2008, Washington, DC. 2008.

NCT00156104. A multicenter, randomized, double-blind, fixed-dose, 6-week trial of the efficacy and safety of asenapine compared with placebo using haloperidol positive control in subjects with an acute exacerbation of schizophrenia. http://clinicaltrials.gov/show/NCT00156104 2008.

Potkin SG, Kane JM, Emsley RA, Naber D, Panagides J. Asenapine in schizophrenia: an overview of clinical trials in the Olympia program. Society of Biological Psychiatry, 63rd Annual Scientific Convention and Meeting, May 1-3, 2008, Washington, DC. 2008.

Kane 2011 *{published data only}*

* Kane JM, Mackle M, Snow-Adami L, Zhao J, Szegedi A, Panagides J. A randomized placebo-controlled trial of asenapine for the prevention of relapse of schizophrenia after long-term treatment. *Journal of Clinical Psychiatry* 2011;**72**(3):349–55.

Kane JM, Mackle M, Snow-Adami L, Zhao J, Szegedi A, Panagides J. Double-blind, placebo-controlled trial of asenapine in prevention of relapse after long-term treatment of schizophrenia. *International Journal of Neuropsychopharmacology* 2010;**13**:223.

Mackle M, Snow-Adami L, Zhao J, Szegedi A, Panagides J. Double-blind, placebo-controlled trial of asenapine in prevention of relapse after long-term treatment of schizophrenia. European Neuropsychopharmacology. 2009; Vol. Conference Start: 20090912 Conference End: 20090916. Conference Publication:, issue Suppl 3:pp S543.

NCT00150176. A randomized, placebo-controlled, double-blind trial of asenapine in the prevention of relapse after long-term treatment of schizophrenia. http://clinicaltrials.gov/show/NCT00150176 2005.

NCT00151424 *{published data only}*

Citrome L. Asenapine for schizophrenia and bipolar disorder: A review of the efficacy and safety profile for this newly approved sublingually absorbed second-generation antipsychotic. *The International Journal of Clinical Practice* 2009;**63**:1762–84.

* NCT00151424. A multicenter, randomized, double-blind, flexible-dose, 6-week trial of the efficacy and safety of asenapine compared with placebo using olanzapine positive control in subjects with an acute exacerbation of schizophrenia. http://clinicaltrials.gov/show/NCT00151424 2005.

Potkin SG, Kane JM, Emsley RA, Naber D, Panagides J. Asenapine in schizophrenia: an overview of clinical trials in the Olympia program. Society of Biological Psychiatry, 63rd Annual Scientific Convention and Meeting, May 1-3, 2008, Washington, DC. 2008.

Szegedi A, Verweij P, Van Duijnhoven W, Mackle M, Cazorla P, Fennema H. Meta-analyses of the efficacy of asenapine for acute schizophrenia: comparisons with placebo and other antipsychotics. *Journal of Clinical Psychiatry* 2012;**73**:1533–40.

NCT00156117 *{published data only}*

Citrome L. Asenapine for schizophrenia and bipolar disorder: a review of the efficacy and safety profile for this newly approved sublingually absorbed second-generation antipsychotic. *The International Journal of Clinical Practice* 2009;**63**:1762–84.

Leucht S, Zhao J. Early improvement as a predictor of treatment response and remission in patients with acute schizophrenia: effects of asenapine. European Neuropsychopharmacology 2013; Vol. 23:S470.

Leucht S, Zhao J. Early improvement as a predictor of treatment response and remission in patients with schizophrenia: a pooled, post-hoc analysis from the asenapine development program. *Journal of Psychopharmacology* 2014;**28**:387–94.

NCT00156117. A multicenter, randomized, double-blind, fixed-dose, 6-week trial of the efficacy and safety of asenapine compared with placebo using olanzapine positive control in subjects with an acute exacerbation of schizophrenia. http://clinicaltrials.gov/show/NCT00156117 2005.

Potkin SG, Kane JM, Emsley RA, Naber D, Panagides J.

Asenapine in schizophrenia: an overview of clinical trials in the Olympia program. Society of Biological Psychiatry, 63rd Annual Scientific Convention and Meeting, May 1-3, 2008, Washington, DC. 2008.
Szegedi A, Verweij P, van Duijnhoven W, Mackle M, Cazorla P, Fennema H. Meta-analyses of the efficacy of asenapine for acute schizophrenia: comparisons with placebo and other antipsychotics. *Journal of Clinical Psychiatry* 2012;**73**: 1533–40.

Potkin 2007 ***{published data only}***
Citrome L. Asenapine for schizophrenia and bipolar disorder: a review of the efficacy and safety profile for this newly approved sublingually absorbed second-generation antipsychotic. *The International Journal of Clinical Practice* 2009;**63**:1762–84.
Fleming K, Potkin SG, Binneman B, Keller D, Alphs L, Panagides J. Effects of asenapine on cognitive function in acute schizophrenia: a placebo- and risperidone-controlled trial. *European Neuropsychopharmacology* 2007;**17**(Suppl 4): S466.
Potkin S, Fleming K, Binneman B, Keller DS, Alphs L, Panagides J. Asenapine improves cognitive function in acute schizophrenia: a placebo- and risperidone- controlled trial. Proceedings of the 160th Annual Meeting of the American Psychiatric Association; 2007 May 19-24; San Diego, CA. 2007.
Potkin S, Fleming K, Binneman B, Keller S. Asenapine cognitive function effects in acute schizophrenia: a placebo- and risperidone-controlled trial. *Schizophrenia Bulletin* 2007;**33**(2):454.
Potkin SG, Cohen M, Baker RA, Jina AS, Nettler S, Alphs L, et al. Asenapine, a novel psychotherapeutic agent with efficacy in positive and negative symptoms during acute episodes of schizophrenia: a randomized, placebo- and risperidone-controlled trial. *Neuropsychopharmacology* 2005; **30**(Suppl 1):S112–3.
Potkin SG, Cohen M, Jina AS, Nettler S, Alphs L, Panagides J. Asenapine efficacy during acute episodes of schizophrenia: a randomized placebo and risperidone controlled trial. Proceedings of the 44th Annual Meeting of the American College of Neuro-Psychopharmacology; 2005 Dec 11-15; Waikoloa, Hawaii. 2005.
Potkin SG, Cohen M, Jina AS, Nettler S, Alphs L, Panagides J. Asenapine efficacy during acute episodes of schizophrenia: a randomized placebo- and risperidone-controlled trial. 13th Biennial Winter Workshop on Schizophrenia Research, February 4-10, 2006, Davos, Switzerland. 2006.
* Potkin SG, Cohen M, Panagides J. Efficacy and tolerability of asenapine in acute schizophrenia: a placebo- and risperidone-controlled trial. *Journal of Clinical Psychiatry* 2007;**68**(10):1492–500.
Potkin SG, Cohen M, Panagides J, Jina A. Asenapine safety and tolerability in acute schizophrenia: a placebo- and risperidone-controlled trial. *European Neuropsychopharmacology* 2006;**16**(Suppl 4):S401.
Potkin SG, Cohen M, Panagides J, Jina AS. Asenapine efficacy in acute schizophrenia: a randomized, placebo- and risperidone-controlled trial. *International Journal of Neuropsychopharmacology* 2006;**9**(Suppl 1):S275.
Potkin SG, Cohen M, Panagides J, Jina AS. Asenapine efficacy, safety, and tolerability in the treatment of acute schizophrenia: a randomized, placebo- and risperidone-controlled trial. *Biological Psychiatry* 2006;**59**(8 Suppl): 154S.
Potkin SG, Cohen M, Panagides J, Jina AS. Asenapine safety and tolerability during acute schizophrenia: a placebo- and risperidone controlled trial. Proceedings of the 159th Annual Meeting of the American Psychiatric Association; 2006 May 20-25, Toronto, Canada. 2006.
Potkin SG, Kane JM, Emsley RA, Naber D, Panagides J. Asenapine in schizophrenia: an overview of clinical trials in the Olympia program. Society of Biological Psychiatry, 63rd Annual Scientific Convention and Meeting, May 1-3, 2008, Washington, DC. 2008.

References to studies excluded from this review

Castle 2013 ***{published data only}***
Castle D, Jensen JKS. Management of depressive symptoms in schizophrenia: a pooled, post hoc analysis from the asenapine development program. (Manuscript submitted for peer-review, journal not currently known).
Castle D, Jensen JKS. Management of depressive symptoms in schizophrenia: a pooled, post hoc analysis from the asenapine development program. *European Neuropsychopharmacology* 2013;**23**:S502–3.

Cazorla 2008 ***{published data only}***
Cazorla P, Panagides J, Alphs L, Kouassi A, Buchanan R. Asenapine versus olanzapine in patients with predominant, persistent negative symptoms of schizophrenia. American Psychiatric Association, 161st Annual Meeting, May 3-8, 2008, Washington, DC. 2008.
Cazorla P, Panagides J, Alphs L, Kouassi A, Buchanan R, Szegedi A. Asenapine versus olanzapine in patients with predominant, persistent negative symptoms of schizophrenia. *International Journal of Neuropsychopharmacology* 2008;**11**(Suppl 1):138–9.

NCT00156065 ***{published data only}***
Meltzer H, Cohen M, Snow-Adami L, Mackle M, Zhao J, Szegedi A, et al. Long-term safety and maintenance of effect of asenapine in patients with acute exacerbation of schizophrenia. *European Neuropsychopharmacology* 2009;**19**: S536–S537.
NCT00156065. A multicenter, double-blind, flexible dose, long-term extension trial of the safety and maintenance of effect of asenapine using a haloperidol positive control in subjects who complete protocol 041023. http://clinicaltrials.gov/show/NCT00156065 2005.

NCT01142596 ***{published data only}***
NCT01142596. Long-term extension trial of asenapine in subjects with schizophrenia (study p06125). http://clinicaltrials.gov/show/NCT01142596 2010.

NCT01190254 *{published data only}*

NCT01190254. Fixed dose efficacy and safety study of asenapine for the treatment of schizophrenia in adolescents (study p05896). http://clinicaltrials.gov/show/NCT01190254 2010.

The National Horizon Scanning Centre 2010 *{published data only}*

The National Horizon Scanning Centre. Asenapine (Saphris) for schizophrenia. The National Horizon Scanning Centre, Department of Public Health and Epidemiology, University of Birmingham. University of Birmingham, 2010.

References to studies awaiting assessment

NCT00156091 *{published data only}*

NCT00156091. A multicenter, double-blind, flexible-dose, long-term extension trial of the safety and maintenance of effect of asenapine using olanzapine positive control in subjects who complete protocols 041021/041022. http://clinicaltrials.gov/show/NCT00156091 2005.

NCT01098110 *{published data only}*

Nct. 6-week trial of the efficacy and safety of asenapine compared to placebo in subjects with an acute exacerbation of schizophrenia (Study P06124). http://clinicaltrials.gov/show/NCT01098110 2010.

References to ongoing studies

NCT01617187 *{published data only}*

NCT01617187. A study of the efficacy and safety of asenapine in participants with an acute exacerbation of schizophrenia (p05688 am2). http://clinicaltrials.gov/show/NCT01617187 2012.

Additional references

Abi-Dargham 2004

Abi-Dargham A. Do we still believe in the dopamine hypothesis? New data bring new evidence. *International Journal of Neuropsychopharmacology* 2004;**7**:S1–5.

Adams 2013

Adams CE, Bergman H, Irving CB, Lawrie S. Haloperidol versus placebo for schizophrenia. *Cochrane Database of Systematic Reviews* 2013, Issue 11. [DOI: 10.1002/14651858.CD003082.pub3; : CD003082]

Addington 1993

Addington D, Addington J, Maticka-Tyndale E. Assessing depression in schizophrenia: the Calgary Depression Scale. *The British Journal of Psychiatry* 1993;**163**:39–44.

Altman 1996

Altman DG, Bland JM. Detecting skewness from summary information. *BMJ* 1996;**313**(7066):1200.

Andreasen 1999

Andreasen NC. A unitary model of schizophrenia. Bleuler's "fragmented phrene" as schizencephaly. *Archives of General Psychiatry* 1999;**56**:781–7.

Ayuso-Mateos 2006

Ayuso-Mateos JL. Global burden of schizophrenia in the year 2000. http://www.who.int/healthinfo/statistics/bod˙schizophrenia.pdf 2006.

Barnes 1989

Barnes TR. A rating scale for drug-induced akathisia. *The British Journal of Psychiatry* 1989;**154**:672–6.

Bishara 2009

Bishara D, Taylor D. Asenapine monotherapy in the acute treatment of both schizophrenia and bipolar I disorder. *Neuropsychiatric Disease and Treatment* 2009;**5**:483–90.

Bland 1997

Bland JM. Statistics notes. Trials randomised in clusters. *BMJ* 1997;**315**:600.

Boissel 1999

Boissel JP, Cucherat M, Li W, Chatellier G, Gueyffier F, Buyse M, et al. The problem of therapeutic efficacy indices. 3. Comparison of the indices and their use [Apercu sur la problematique des indices d'efficacité thérapeutique, 3: comparaison des indices et utilisation. Groupe d'Etude des Indices D'efficacité]. *Thérapie* 1999;**54**(4):405–11. [PUBMED: 10667106]

Campbell 1999

Campbell M, Young PI, Bateman DN, Smith JM, Thomas SHL. The use of atypical antipsychotics in the management of schizophrenia. *British Journal of Clinical Pharmacology* 1999;**47**:13–22.

Citrome 2009

Citrome L. Asenapine for schizophrenia and bipolar disorder: a review of the efficacy and safety profile for this newly approved sublingually absorbed second-generation antipsychotic. *The International Journal of Clinical Practice* 2009;**63**:1762–84.

Crow 1980

Crow TJ. Molecular pathology of schizophrenia: more than one disease process?. *British Medical Journal* 1980;**280**:66–8.

Davis 2003

Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. *Archives of General Psychiatry* 2003;**60**:553–64.

Deeks 2000

Deeks J. Issues in the selection for meta-analyses of binary data. Proceedings of the 8th International Cochrane Colloquium; 2000 Oct 25-28; Cape Town. Cape Town: The Cochrane Collaboration, 2000.

Deeks 2011

Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Divine 1992
Divine GW, Brown JT, Frazier LM. The unit of analysis error in studies about physicians' patient care behavior. *Journal of General Internal Medicine* 1992;**7**(6):623–9.

Donner 2002
Donner A, Klar N. Issues in the meta-analysis of cluster randomized trials. *Statistics in Medicine* 2002;**21**:2971–80.

Duggan 2005
Duggan L, Fenton M, Rathbone J, Dardennes R, El-Dosoky A, Indran S. Olanzapine for schizophrenia. *Cochrane Database of Systematic Reviews* 2005, Issue 2. [DOI: 10.1002/14651858.CD001359.pub2; : CD001359]

Egger 1997
Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**:629–34.

Elbourne 2002
Elbourne D, Altman DG, Higgins JPT, Curtina F, Worthingtond HV, Vaile A. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**(1):140–9.

EMA 2014
European Medicines Agency. Sycrest: EPAR - Product information. http://www.ema.europa.eu/docs/en˙GB/document˙library/EPAR˙-˙Product˙Information/human/001177/WC500096895.pdf 2014.

Emsley 2013
Emsley R, Fleischhacker WW. Is the ongoing use of placebo in relapse-prevention clinical trials in schizophrenia justified?. *Schizophrenia Research* 2013;**150**:427–33.

FDA 2013
Food, Drug Administration. Saphris (asenapine) prescribing information. http://www.accessdata.fda.gov/drugsatfda˙docs/label/2013/022117s012lbl.pdf 2013.

Fioravanti 2005
Fioravanti M, Carlone O, Vitale B, Cinti ME, Clare L. A meta-analysis of cognitive deficits in adults with a diagnosis of schizophrenia. *Neuropsychology Review* 2005;**15**:73–95.

Furukawa 2006
Furukawa TA, Barbui C, Cipriani A, Brambilla P, Watanabe N. Imputing missing standard deviations in meta-analyses can provide accurate results. *Journal of Clinical Epidemiology* 2006;**59**(7):7–10.

Gulliford 1999
Gulliford MC. Components of variance and intraclass correlations for the design of community-based surveys and intervention studies: data from the Health Survey for England 1994. *American Journal of Epidemiology* 1999;**149**: 876–83.

Guy 1976
Guy W. *ECDEU Asessment Manual for Psychopharmacology*. Rockville, 1976.

Hedlund 2004
Hedlund PB, Sutcliffe JG. Functional, molecular and pharmacological advances in 5-HT7 receptor research. *Trends in Pharmacological Sciences* 2004;**25**:481–6.

Higgins 2003
Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**: 557–60.

Higgins 2011a
Higgins JPT, Deeks JJ (editors). Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org..

Higgins 2011b
Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Higgins 2011c
Higgins JPT, Deeks JJ, Altman DG (editors). Chapter 16: Special topics in statistics. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011.. Available from www.cochrane-handbook.org.

Hutton 2009
Hutton JL. Number needed to treat and number needed to harm are not the best way to report and assess the results of randomised clinical trials. *British Journal of Haematology* 2009;**146**(1):27–30.

Kay 1986
Kay SR, Opler LA, Fiszbein A. *Positive and Negative Syndrome Scale (PANSS) Manual*. North Tonawanda, NY: Multi-Health Systems, 1986.

Kay 1987
Kay SR, Fiszbein A, Opfer LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin* 1987;**13**:261–76.

Kohler 2007
Kohler S, Van Os J, De Graaf R, Vollebergh W, Verhey F, Krabbendam L. Psychosis risk as a function of age at onset. *Social Psychiatry and Psychiatric Epidemiology* 2007;**4**: 288–94.

Kumar 2012
Kumar A, Narayan M, Raja H, Mathen Manoj J. Asenapine versus typical antipsychotics for schizophrenia. *Cochrane Database of Systematic Reviews* 2012, Issue 11. [DOI: 10.1002/14651858.CD010230; : CD010230]

Lankappa 2012
Lankappa S, Gandhi R. Quetiapine versus placebo for schizophrenia. *Cochrane Database of Systematic Reviews*

2012, Issue 7. [DOI: 10.1002/14651858.CD009935; : CD009935]

Lehmann 1997
Lehmann HE, Ban TA. The history of the psychopharmacology of schizophrenia. *Canadian Journal of Psychiatry* 1997;**42**:152–62.

Leon 2006
Leon AC, Mallinckrodt CH, Chuang-Stein C, Archibald DG, Archer GE, Chartier K. Attrition in randomized controlled clinical trials: methodological issues in psychopharmacology. *Biological Psychiatry* 2006;**59**(11): 1001–5. [PUBMED: 16905632]

Leucht 2005
Leucht S, Kane JM, Kissling W, Hamann J, Etschel E, Engel RR. What does the PANSS mean?. *Schizophrenia Research* 2005;**79**(2-3):231–8. [PUBMED: 15982856]

Leucht 2013
Leucht S, Zhao J. Early improvement as a predictor of treatment response and remission in patients with acute schizophrenia: effects of asenapine. European Neuropsychopharmacology 2013; Vol. 23:S470.

Leucht 2014
Leucht S, Zhao J. Early improvement as a predictor of treatment response and remission in patients with schizophrenia: a pooled, post-hoc analysis from the asenapine development program. *Journal of Psychopharmacology* 2014;**28**:387–94.

Liddle 1987
Liddle PF. The symptoms of chronic schizophrenia. A re-examination of the positive-negative dichotomy. *British Journal of Psychiatry* 1987;**151**:145–51.

Lieberman 2004
Lieberman JA. Managing anticholinergic side effects. *The Primary Care Companion to the Journal of Clinical Psychiatry* 2004;**6**:20–3.

Marder 1997
Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: Combined results of the North American trials. *Journal of Clinical Psychiatry* 1997;**58**:538–46.

Marshall 2000
Marshall M, Lockwood A, Bradley C, Adams C, Joy C, Fenton M. Unpublished rating scales: a major source of bias in randomised controlled trials of treatments for schizophrenia. *British Journal of Psychiatry* 2000;**176**: 249–52.

McGrath 2008
McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiological Reviews* 2008;**30**:67–76.

Meltzer 1999
Meltzer HY. The role of serotonin in antipsychotic drug action. *Neuropsychopharmacology* 1999;**21**:106S–15S.

Moher 2010
Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;**340**:c869.

Muench 2010
Muench J, Hamer AN. Adverse effects of antipsychotic medications. *American Family Physician* 2010;**81**:617–22.

Munetz 1988
Munetz MR, Benjamin S. How to examine patients using the Abnormal Involuntary Movement Scale. *Hospital & Community Psychiatry* 1988;**39**:1172–7.

Nicholson 1983
Nicholson AN. Antihistamines and sedation. *The Lancet* 1983;**322**:211–2.

Overall 1962
Overall JE, Gorham DR. The brief psychiatric rating scale. *Psychological Reports* 1962;**10**:799–812.

Preda 2010
Preda A, Faziola L. Asenapine versus other atypical antipsychotics for schizophrenia. *Cochrane Database of Systematic Reviews* 2010, Issue 12. [DOI: 10.1002/14651858.CD008902; : CD008902]

Rattehalli 2010
Rattehalli Ranganath D, Jayaram Mahesh B, Smith M. Risperidone versus placebo for schizophrenia. *Cochrane Database of Systematic Reviews* 2010, Issue 1. [DOI: 10.1002/14651858.CD006918.pub2; : CD006918]

Saha 2005
Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. *PLoS Medicine* 2005;**2**:0413–33.

Schünemann 2011
Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, et al. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org. The Cochrane Collaboration, 2011.

Shahid 2009
Shahid M, Walker GB, Zorn SH, Wong E. Asenapine: a novel psychopharmacologic agent with a unique human receptor signature. *Journal of Psychopharmacology* 2009;**23**: 65–73.

Simpson 1970
Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. *Acta Psychiatrica Scandinavica* 1970;**45**:11–9.

Siris 2000
Siris SG. Depression in schizophrenia: perspective in the era of "atypical" antipsychotic agents. *American Journal of Psychiatry* 2000;**157**:1379–89.

Sterne 2011
Sterne JAC, Egger M, Moher D (editors). Chapter 10: Addressing reporting biases. In: Higgins JPT, Green

S (editors). *Cochrane Handbook for Systematic Reviews of Intervention.* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Stoner 2012
Stoner SC, Pace HA. Asenapine: a clinical review of a second-generation antipsychotic. *Clinical Therapeutics* 2012;**34**:1023–40.

Storosum 1998
Storosum JG, Elferink AJA, Van Zwieten BJ. Schizophrenia: do we really need placebo-controlled studies?. *European Neuropsychopharmacology* 1998;**8**:279–86.

Svensson 2003
Svensson TH. a-Adrenoceptor modulation hypothesis of antipsychotic atypicality. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 2003;**27**: 1145–58.

Sycrest 2014
Sycrest. Sycrest patient information leaflet. http://www.sycrest.co.uk/siteuploads/PIL.pdf 2014.

Szegedi 2012
Szegedi A, Verweij P, van Duijnhoven W, Mackle M, Cazorla P, Fennema H. Meta-analyses of the efficacy of asenapine for acute schizophrenia: Comparisons with placebo and other antipsychotics. *Journal of Clinical Psychiatry* 2012;**73**: 1533–40.

Ukoumunne 1999
Ukoumunne OC, Gulliford MC, Chinn S, Sterne JAC, Burney PGJ. Methods for evaluating area-wide and organisation-based intervention in health and health care: a systematic review. *Health Technology Assessment* 1999;**3**(5): 1–75.

van Os 2008
Van Os J, Rutten BPF, Poulton R. Gene-environment interactions in schizophrenia: review of epidemiological findings and future directions. *Schizophrenia Bulletin* 2008; **34**:1066–82.

Walker 2004
Walker E, Kestler L, Bollini A, Hochman KM. Schizophrenia: etiology and course. *Annual Review of Psychology* 2004;**55**:401–30.

WHO 2014
World Health Organization. Schizophrenia. http://www.who.int/mental˙health/management/schizophrenia/en/ 2014.

Worrel 2000
Worrel JA, Marken PA, Beckman SE, Ruehter VL. Atypical antipsychotic agents: a critical review. *American Journal of Health-System Pharmacy* 2000;**57**:238–55.

Xia 2009
Xia J, Adams CE, Bhagat N, Bhagat V, Bhoopathi P, El-Sayeh H, et al. Loss to outcomes stakeholder survey: the LOSS study. *Psychiatric Bulletin* 2009;**33**(7):254–7.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Chapel 2009

Methods	Allocation: random allocation. Blindness: double-blind. Duration: 16 days. Funding: Organon - a part of Schering-Plough Corporation and Pfizer Inc Country: six sites in the United States and one site in South Africa
Participants	Diagnosis: schizophrenia or schizoaffective disorder (DSM-IV) N: 148. Age: 18 to 65 years (mean age 42.6 years). Sex: 114 men and 34 women. History: no details.
Interventions	1. Asenapine: 5 mg for 10 days followed by 10 mg for six days (BID) N = 38 2. Asenapine: 15 mg for 10 days followed by 20 mg for six days (BID) N = 38 3. Quetiapine: 375 mg for 16 days N = 37. 4. Placebo: for 16 days N=35.
Outcomes	Usable: Adverse effects (QTc prolongation-incidence, ECG, blood samples) Leaving study early. Unusable: Adverse effects (QTc average change; and blood sample data not fully reported for placebo; weight: only reported baseline data)
Notes	Did not use data for quetiapine trial arm.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomised" - but no further details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind" - but no further description provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided.

Chapel 2009 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	From 148 participants, "Twenty- three patients withdrew before day 10 (eight owing to adverse events), and 11 additional patients withdrew before day 16 (one owing to an adverse event)" No description of how the loss was addressed in the analysis
Selective reporting (reporting bias)	High risk	Endpoint population characteristics not provided for QTc and weight
Other bias	High risk	"Financial support for this work was provided by Pfizer, Inc and Schering - Plough" The authors were employed by Schering-Plough or Pfizer, Inc at the time of trial

Kane 2010

Methods	Allocation: random allocation; (1:1:1:1 distribution). Blindness: double-blind. Duration: six-week trial. Funding: sponsored by Organon, Pfizer Inc. Country: 43 sites in five countries (United States, Russia, India, Romania & Canada)
Participants	Diagnosis: acute exacerbated schizophrenia (DSM-IV-TR). 91% diagnosis of paranoid schizophrenia. N: 458. Age: mean age range - 37 to 40 years. Sex: 52% male. History: mean age at onset of illness is 26 years (range 6 - 60 years) 50% exhibited current or past prominent negative symptoms. 54% had four or more previous episodes of acute schizophrenia requiring hospitalisation 29% had a history of one or more suicide attempts. Majority of patients in each treatment group had a history of smoking within the past six months
Interventions	1. Asenapine (5 mg, BID) N = 114. 2. Asenapine (10 mg, BID) N = 106. 3. Placebo N = 123. 4. Haloperidol (4 mg, BID) N = 115.
Outcomes	Usable Global State (CGI-S, CGI-I; concomitant drugs). Mental State (change in PANSS total score; CDSS). Adverse effects (AIMS, BAS, SAS; fasting glucose; prolactin; weight; deaths) Leaving the study early. Unusable Mental state (ISST - no data reported).

	Cognitive functioning (CNS vital signs - no data reported). Adverse effects (weekly lab assessments; ECG - insufficient data reported) Quality of life (QLS, Q-LSQ, PETIT - no data reported). Readiness to discharge (no data reported).
Notes	Did not use data for haloperidol trial arm. For follow up: patients who complete six-week trial given option to continue for 52-week trial (NCT00156065).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised" - but no further details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind" - but no further description provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	"In all, 272 patients (61% of the ITT population) completed the study" ITT population and LOCF and MMRM method of analysis were used
Selective reporting (reporting bias)	Low risk	Most outcomes reported with mean and standard deviations.
Other bias	High risk	Four of the authors were employed at Merck or Pfizer, Inc at the time of trial. The lead author was affiliated with Bristol - Myers Squibb, Otsuka Pharmaceuticals, Eli-Lilly and Co, Janssen, Johnson & Johnson PRD, MDS Pharma Services, Pfizer Inc, Solvay Pharmaceutical Inc, Wyeth Pharmaceuticals, Lundbeck, Vanda Pharmaceuticals, Astra- Zeneca, Cephalon, Dainippon Sumitomo, Glaxo Smith Kline, Intracellular therapeutics, PGxHealth, Proteus, Takeda and Schering- Plough "....funded by Schering- Plough Corporation, now Merck & Co, Inc, (Whitehouse Station, NJ, USA)"

Kane 2011

Methods	Allocation: random allocation. Blindness: double-blind. Duration: 52-week extended trial. Two phases: 26 weeks of open label treatment of asenapine; 26 weeks of double-blind treatment (where they continued with asenapine or were switched to placebo) Funding: Merck Country: United States, Russian Federation, Ukraine, India, Latvia and Croatia
Participants	Diagnosis: schizophrenia (DSM-IV-TR) N: 386 Age: range 18 to 78 years. Sex: asenapine men (N = 105), asenapine women (N = 89), placebo men (N = 116), placebo women (N = 76) History: more than one prior acute schizophrenia episode during the preceding three years and schizophrenia requiring continuous anti-psychotic treatment for more than one year preceding screening
Interventions	1. Asenapine (10 mg BID) N = 194 2. Placebo N = 192
Outcomes	Usable: Global State (CGI-S; relapse; concomitant drugs). Mental State (PANSS total score, PANSS Marder factor scores; mood - CDSS) Adverse effects (weight, incidence of EPS - AIMS, BAS, SAS). Leaving the study early. Unusable: Global State (time to relapse/impending relapse - no data reported for asenapine reported) Mental state (Modified ISST - no data reported). Adverse effects (average change - no SDs reported for BAS, AIMS, SAS; ECG; hyperprolactinaemia) Leaving the study early (time to early discontinuation - no average value reported for each group)
Notes	Subgroup analyses reported calculating incidence of concomitant medication used in patients who experienced relapse/impending relapse; not to be included in meta-analyses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised" - but no further details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind". "asenapine and placebo sublingual tablets were identical in appearance" "neither patients nor sites were aware of the

		tablet identity" Probably done.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Incidence of relapse: "Determination of relapse/impending relapse was based on investigator judgement in 75%" Possibility of biased judgement - high risk. All other outcomes: no details provided - unclear risk.
Incomplete outcome data (attrition bias) All outcomes	High risk	Of 386 patients entered "only 207" completed the study. They used ITT population "Period end point is the last non-missing post baseline assessment on or before last double blind dose date plus 3d" This suggests that LOCF method of analysis was used.
Selective reporting (reporting bias)	High risk	Data for time to relapse reported only for placebo and not for asenapine No standard deviations reported for specific adverse effects
Other bias	High risk	"This study was funded by Merck and Pfizer Inc". All of the authors were either affiliated with or employed by Merck or Schering-Plough

NCT00151424

Methods	Allocation: random allocation. Blindness: double-blind. Duration: six-week trial Funding: Organon. Country: not provided.
Participants	Diagnosis: schizophrenia. N: treated sample: 275. Age: over 18 years old. Sex: men and women. History: patients currently experiencing acute exacerbation of schizophrenia
Interventions	1. Asenapine (5 - 10 mg BID) N = 90. 2. Olanzapine (10 - 20 mg QD) N = 92. 3. Placebo N = 93.
Outcomes	Usable: Adverse effects (EPS, deaths, weight gain). Leaving the study early.

NCT00151424 (*Continued*)

	Unusable: Global state (CGI-S, CGI-I - no data reported). Mental state (anxiety, depression, suicidal thinking - no data reported; PANSS - odds ratios only, not able to input to generic inverse variance without faulting - statistical advice being sought) Cognitive functioning (no data reported). Functioning (no data reported). Adverse effects (EPS, laboratory parameters, vital signs, weight, ECGs - no data reported) Quality of life (no data reported). Readiness to discharge (no data reported).
Notes	Three study authors contacted regarding further information about trial: 1. Prof. Potkin emailed twice, awaiting response. 2. Dr. Szegedi emailed once using Merck address, failed to deliver, unable to locate current email address 3. Prof. Leucht provided contact details of colleagues considered better suited to provide information, awaiting response from provided contacts

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised" - but no further details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind - no further description.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	LOCF method was used for analysis.
Selective reporting (reporting bias)	High risk	No data reported for multiple outcomes: global state (CGI-S, CGI-I), mental state (PANSS, anxiety, depression, suicidal thinking), cognitive functioning, functioning, specific adverse events, quality of life, readiness to discharge
Other bias	High risk	Sponsored by Organon and Pfizer Inc. Unpublished trial.

NCT00156117

Methods	Allocation: random allocation. Blindness: double blind. Duration: six-week trial. Funding: Merck Sharp & Dohme Corp. Country: not provided.
Participants	Diagnosis: schizophrenia. N: ITT sample: 386. Age: over 18 years old. Sex: men and women. History: currently suffering from an acute exacerbation of schizophrenia
Interventions	1. Asenapine (5 mg BID) N = 102. 2. Asenapine (10 mg BID) N = 96. 3. Olanzapine (15 mg QD) N = 95. 4. Placebo N = 93.
Outcomes	Usable: Mental state (PANSS). Leaving study early Unusable (no data reported): Global state (CGI-S, CGI-I). Mental state (PANSS, anxiety, suicidal thinking). Cognitive functioning. Functioning. Adverse effects (EPS, laboratory parameters, vital signs, weight, ECGs) Quality of life. Readiness to discharge.
Notes	Four authors contacted regarding further information regarding trial: 1. Prof. Potkin emailed twice, awaiting response. 2. Dr. Szegedi emailed once using Merck address, failed to deliver, unable to locate current email address 3. Prof. Leucht graciously provided contact details of colleagues considered better suited to provide information, awaiting response from provided contacts 4. Prof. Castle graciously provided manuscript submitted for peer review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised" - but no further details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-Blind (subject, caregiver, investigator, outcomes assessor)" No further description.

NCT00156117 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT sample was used for the study.
Selective reporting (reporting bias)	High risk	No data reported for multiple outcomes: global state (CGI-S, CGI-I), mental state (PANSS, anxiety, suicidal thinking), cognitive functioning, functioning, specific adverse events, quality of life, readiness to discharge
Other bias	High risk	The study is funded by Schering-Plough. Unpublished trial.

Potkin 2007

Methods	Allocation: random allocation. Blindness: double-blind; double-dummy design: asenapine patients also received placebo BID Duration: six-week trial. Funding: Organon Pharmaceuticals Inc.; Pfizer Inc. Country: 21 sites in United States.
Participants	Diagnosis: schizophrenia (DSM-IV); subtypes (including paranoid, disorganized, undifferentiated) N: randomised 180*. Age: over 18 years old. Sex: ~78% men, ~22% women. History: duration of present episode: Up to one month: 34 (58%) asenapine, 39 (63%) placebo. One to six months: 21 (36%) asenapine, 16 (26%) placebo. Over six months: 3 (5%) asenapine, 6 (10%) placebo. Not specified or not obtained: 1 (2%) asenapine, 1 (2%) placebo
Interventions	1. Asenapine (5 mg BID - titrated) sublingual + oral placebo (BID) N = 59 2. Placebo (BID) oral + sublingual placebo (BID) N = 62. 3. Risperidone (3 mg BID) oral + oral placebo (BID) N = 59.*
Outcomes	Usable: Global State (use of concomitant drugs). Adverse effects (ECG assessments, prolactin, glucose, incidence of QTc prolongation, sinus tachycardia, weight gain) Leaving the study early. Unusable: Global state (CGI-S - loss of data > 50%; adherence to trial - no data reported)

	Mental state (PANSS - loss of data > 50%). Cognitive functioning (neurocognitive battery - no data reported) Adverse effects (blood pressure, heart rate, temperature, respiratory rate, cholesterol, triglycerides, QTc, weight gain - data without SDs, SEs or P values; EPS - data without SDs, SEs, or P values for BAS, SAS, AIMS)
Notes	*Did not use risperidone trial arm.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised" - but no further details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind" "In this double-dummy design, asenapine-treated patients also received oral placebo BID...and patients in the placebo-control group received oral and sublingual placebo BID" Probably done.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	"For the intention-to-treat population... the primary outcome measure (change from baseline in PANSS total score with asenapine vs. placebo at end point or last observation carried forward [LOCF]) was analysed using least-squares means based on two-way analysis of variance, with treatment and center as factors. For secondary outcome measures, similar comparisons were made for asenapine versus placebo..." Discontinuation rate > 50%; ITT population and LOCF method of analysis were used
Selective reporting (reporting bias)	High risk	No SDs reported for changes in PANSS total, positive, negative and general psychopathology scores; changes in CGI-S scores; actual weight gain, changes in total cholesterol, fasting triglycerides and QTc Only adverse events in ≧10% patients of

Potkin 2007 (*Continued*)

		any treatment group (of treated population) were reported
Other bias	High risk	"Financial support for this trial was provided by Organon Pharmaceuticals USA Inc" Funded and supported by Organon Pharmaceuticals USA/International Inc. and Pfizer Inc

General abbreviations
BID - bis in die (twice daily)
CNS - Central nervous system
DSM-IV - Diagnostic and Statistical Manual - Fourth Edition
DSM-IV-TR - Diagnostic and Statistical Manual - Fourth Edition, Text Revision
ECG - Electrocardiogram
EPS - Extrapyramidal symptoms
ITT - Intention-to-treat
LOCF - Last observation carried forward
MMRM - Mixed model of repeated measures
QD - quaque die (everyday)
SD - Standard deviation
SE - Standard error
Scales
AIMS - Abnormal involuntary movement scale
BAS - Barnes akathisia scale
CDSS - The Calgary depression scale for schizophrenia
CGI-I - Clinical global impression - Improvement scale
CGI-S - Clinical global impression - Severity scale
ISST - InterSePT scale for suicidal thinking
PANSS - Positive and negative syndrome scale
PETIT - Personal evaluation of transitions in treatment
QLS - The quality of life scale for schizophrenia
Q-LES-Q - Quality of life enjoyment and satisfaction questionnaire
Q-LSQ - Quality of life in depression scale
RDQ - Readiness to discharge questionnaire
SAS - Simpson-Angus Scale

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

Study	Reason for exclusion
Castle 2013	Allocation: not randomised, pooled analysis of three asenapine vs. placebo RCTs (Potkin 2007; Kane 2010; NCT00156117).
Cazorla 2008	Allocation: random allocation Participants: adults (over 18 years old) diagnosed with schizophrenia Intervention: asenapine versus olanzapine; no placebo control
NCT00156065	Allocation: random allocation Participants: adults (over 18 years old) diagnosed with schizophrenia Intervention: asenapine 5 - 10 mg BID versus asenapine 5 - 10 mg plus placebo BID versus haloperidol 2 - 8 mg BID; no placebo control
NCT01142596	Allocation: random allocation Participants: adults (over 20 years old) diagnosed with schizophrenia Intervention: asenapine 5 mg BID versus asenapine 10 mg BID; no placebo control
NCT01190254	Allocation: random allocation Participants: adolescents (12 to 18 years old) diagnosed with schizophrenia, not adults
The National Horizon Scanning Centre 2010	Allocation: not randomised; summary of information from clinical trials of asenapine

BID - Bis in die (twice daily)
RCT - Randomised controlled trial.

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

NCT00156091

Methods	Allocation: random allocation Blindness: double-blind Duration: 52-week trial Funding: Merck Sharp & Dohme Corp. Country: not provided
Participants	Diagnosis: schizophrenia (DSM-IV) N: 260 Age: over 18 years old Sex: men and women History: no details
Interventions	1. Asenapine (5 or 10 mg BID) 2. Olanzapine (20 mg QD) 3. Placebo

NCT00156091 (*Continued*)

Outcomes	Global State Mental State (mean change in PANSS total score; CDSS). Cognitive functioning Functioning Adverse effects (vital signs, EPS, ISST, weight, ECG, physical exams and lab tests) Quality of life (QLS, Q-LES-Q, PETIT).
Notes	NCT00156091

NCT01098110

Methods	Allocation: random allocation Blindness: double-blind Duration: six week trial Funding: Schering - Plough Country: not provided
Participants	Diagnosis: schizophrenia (DSM-IV) N: 528 Age: 20-64 years Sex: men and women History: no details
Interventions	1. Asenapine (5 or 10 mg BID) 2. Olanzapine (20 mg QD) 3. Placebo
Outcomes	Mental state (change in PANSS total score)
Notes	NCT01098110

BID - bis in die (twice daily).
CDSS - The Calgary depression scale for schizophrenia.
DSM-IV - Diagnostic and Statistical Manual - fourth edition.
ECG - Electrocardiogram.
EPS - Extrapyramidal symptoms.
ISST - InterSePT scale for suicidal thinking.
PANSS - Positive and negative syndrome scale.
PETIT- Personal evaluation of transitions in treatment.
QD - quaque die (everyday).
Q-LES-Q - Quality of life enjoyment and satisfaction questionnaire.
QLS - The quality of life scale for schizophrenia.

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

NCT01617187

Trial name or title	A study of the efficacy and safety of asenapine in participants with an acute exacerbation of schizophrenia. NCT01617187
Methods	Allocation: random allocation Blindness: double-blind Duration: six-week trial Funding: Merck Country: Croatia & Ukraine
Participants	Diagnosis: schizophrenia (DSM-IV) N: estimated 354 Age: over 18 years old Sex: men and women History: no details
Interventions	1. Asenapine (2.5 mg BID) 2. Asenapine (5 mg BID) 3. Placebo 4. Olanzapine (15 mg QD)
Outcomes	Mental State (Change in PANSS total score; number of participants with greater than or equal to 30% reduction) Global State (Change in CGI-S score).
Starting date	Study start date: December 2012.
Contact information	Toll Free Number: 1888-577-8839
Notes	

BID - bis in die (twice daily).
CGI-S - Clinical global impression - Severity scale.
DSM-IV - Diagnostic and Statistical Manual - fourth edition.
PANSS - Positive and Negative Syndrome Scale.
QD - quaque die (everyday).

DATA AND ANALYSES

Comparison 1. ASENAPINE versus PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global state: 1. No clinically important change (CGI-I) - short-term (up to 12 weeks)	1	336	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.68, 0.97]
2 Global state: 2. Average change score (CGI-S, high=poor)	2	718	Mean Difference (IV, Fixed, 95% CI)	-0.50 [-0.62, -0.37]
2.1 short-term (up to 12 weeks)	1	336	Mean Difference (IV, Fixed, 95% CI)	-0.35 [-0.55, -0.15]
2.2 medium-term (13 to 26 weeks)	1	382	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-0.77, -0.43]
3 Global state: 3. Relapse - medium-term (13 to 26 weeks)	1	386	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.18, 0.40]
4 Global state: 4. Use of any concomitant medication	2	726	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.76, 0.96]
4.1 short-term	1	340	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.74, 0.97]
4.2 medium-term	1	386	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.71, 1.07]
5 Global state: 5. Use of specific concomitant medication	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 acetaminophen - short-term	1	340	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.48, 1.12]
5.2 antiparkinsonian medication - short-term	2	461	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.78, 1.88]
5.3 benzatropine - short-term	1	340	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.43, 2.57]
5.4 ibuprofen - short-term	1	340	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.30, 1.22]
5.5 lorazepam - short-term	2	461	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.71, 1.02]
5.6 lorazepam - medium-term	1	386	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.16, 1.27]
5.7 trihexyphenidyl - short-term	1	340	Risk Ratio (M-H, Fixed, 95% CI)	1.70 [0.83, 3.50]
5.8 trihexyphenidyl - medium-term	1	386	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.19, 2.30]
5.9 zolpidem - short-term	2	461	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.71, 1.40]
5.10 zolpidem - medium-term	1	386	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.07, 1.61]
6 Mental state: 1. No clinically important change (PANSS) - short-term	1	336	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.59, 0.86]
7 Mental state: 2. Average change in total score (baseline-to-endpoint) (PANSS, high=poor)	3	1009	Mean Difference (IV, Fixed, 95% CI)	-7.24 [-9.18, -5.29]
7.1 PANSS total score - short-term	2	627	Mean Difference (IV, Fixed, 95% CI)	-3.77 [-6.50, -1.04]
7.2 PANSS total score - medium-term	1	382	Mean Difference (IV, Fixed, 95% CI)	-10.80 [-13.57, -8.03]

8 Mental state: 3. Average change score (baseline-to-endpoint) (various scales, high=poor)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 CDSS total score - short-term	1	336	Mean Difference (IV, Fixed, 95% CI)	-0.86 [-1.62, -0.10]
8.2 CDSS total score - medium-term	1	382	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-1.25, -0.15]
8.3 PANSS Marder anxiety/ depression factor score - short-term	1	336	Mean Difference (IV, Fixed, 95% CI)	-0.55 [-1.26, 0.16]
8.4 PANSS Marder anxiety/ depression factor score - medium-term	1	382	Mean Difference (IV, Fixed, 95% CI)	-1.4 [-1.95, -0.85]
8.5 PANSS Marder disorganized thought factor score - short-term	1	336	Mean Difference (IV, Fixed, 95% CI)	-1.25 [-2.20, -0.30]
8.6 PANSS Marder disorganized thought factor score - medium-term	1	382	Mean Difference (IV, Fixed, 95% CI)	-2.4 [-2.95, -1.85]
8.7 PANSS Marder hostility/ excitement factor score - short-term	1	336	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-1.21, 0.21]
8.8 PANSS Marder hostility/ excitement factor score - medium-term	1	382	Mean Difference (IV, Fixed, 95% CI)	-2.0 [-2.55, -1.45]
8.9 PANSS Marder negative factor score - short-term	1	336	Mean Difference (IV, Fixed, 95% CI)	-1.10 [-2.29, 0.09]
8.10 PANSS Marder negative factor score - medium-term	1	382	Mean Difference (IV, Fixed, 95% CI)	-1.7 [-2.53, -0.87]
8.11 PANSS Marder positive factor score - short-term	1	336	Mean Difference (IV, Fixed, 95% CI)	-2.40 [-3.83, -0.97]
8.12 PANSS Marder positive factor score - medium-term	1	382	Mean Difference (IV, Fixed, 95% CI)	-3.4 [-4.23, -2.57]
9 Adverse effects: 1. Incidence of serious adverse effects	4	1030	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.42, 1.00]
9.1 short-term	3	644	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.63, 2.00]
9.2 medium-term	1	386	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.14, 0.63]
10 Adverse effects: 2. Incidence of any adverse effects	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 any adverse effects - short-term	2	461	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.89, 1.11]
10.2 any treatment-emergent adverse effects - medium-term	1	386	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.68, 1.01]
10.3 any treatment-related adverse effects - short-term	1	340	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.91, 1.52]
10.4 any treatment-related adverse effects - medium-term	1	386	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.59, 1.19]
11 Adverse effects: 3. Incidence of adverse effects by severity - short-term	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 mild adverse effects	1	340	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.66, 1.18]

11.2 moderate adverse effects	1	340	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.71, 1.42]
11.3 severe adverse effects	3	644	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.80, 2.91]
12 Adverse effects: 4. Specific adverse effects - 4.1. Cardiovascular: incidence - short-term	2		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
12.1 QTc interval >450ms	2	232	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.07, 0.05]
12.2 sinus tachycardia	1	121	Risk Difference (M-H, Fixed, 95% CI)	0.01 [-0.11, 0.12]
13 Adverse effects: 4. Specific adverse effects - 4.2. Gastrointestinal: incidence - short-term	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 clinically significant gamma-glutamyl transpeptidase levels	1	183	Risk Ratio (M-H, Fixed, 95% CI)	3.62 [1.24, 10.57]
13.2 clinically significant alanine aminotransferase levels	1	183	Risk Ratio (M-H, Fixed, 95% CI)	2.58 [1.20, 5.56]
13.3 constipation	1	121	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.36, 3.08]
13.4 dyspepsia	1	121	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.24, 2.98]
13.5 vomiting	2	461	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.61, 2.84]
14 Adverse effects: 4. Specific adverse effects - 4.3. Metabolic: incidence	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 clinically significant fasting glucose levels - short-term	3	641	Risk Ratio (M-H, Fixed, 95% CI)	2.24 [1.06, 4.75]
14.2 clinically significant fasting triglycerides levels - short-term	1	183	Risk Ratio (M-H, Fixed, 95% CI)	8.27 [1.06, 64.77]
14.3 clinically significant HbA1C levels - short-term	1	183	Risk Ratio (M-H, Fixed, 95% CI)	7.23 [0.38, 138.03]
14.4 clinically significant hyperprolactinaemia - short-term	2	458	Risk Ratio (M-H, Fixed, 95% CI)	3.28 [0.97, 11.06]
14.5 clinically significant hyperprolactinaemia - medium-term	1	386	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.21, 1.86]
14.6 clinically significant weight gain - short-term	3	623	Risk Ratio (M-H, Fixed, 95% CI)	3.48 [1.19, 10.15]
14.7 clinically significant weight gain - medium-term	1	386	Risk Ratio (M-H, Fixed, 95% CI)	6.93 [0.86, 55.77]
14.8 clinically significant weight loss - short-term	1	340	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.14, 5.02]
14.9 clinically significant weight loss - medium-term	1	386	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.13, 0.81]
14.10 weight gain - medium-term	1	386	Risk Ratio (M-H, Fixed, 95% CI)	1.84 [0.75, 4.51]
14.11 weight loss - medium-term	1	386	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.18, 1.03]

15 Adverse effects: 4. Specific adverse effects - 4.4. Metabolic: average change in prolactin levels (μg/L) (baseline-to-endpoint) - short-term	1	340	Mean Difference (IV, Fixed, 95% CI)	6.01 [-3.35, 15.37]
16 Adverse effects: 4. Specific adverse effects - 4.5. Metabolic: average change in weight (kg) (baseline-to-endpoint)	2	726	Mean Difference (IV, Fixed, 95% CI)	1.15 [0.54, 1.76]
16.1 short-term	1	340	Mean Difference (IV, Fixed, 95% CI)	1.05 [-0.03, 2.13]
16.2 medium-term	1	386	Mean Difference (IV, Fixed, 95% CI)	1.2 [0.46, 1.94]
17 Adverse effects: 4. Specific adverse effects - 4.6. Other specific adverse effects: incidence	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 agitation - short-term	2	461	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.28, 0.89]
17.2 agitation - medium-term	1	386	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.12, 1.11]
17.3 akathisia - short-term	1	340	Risk Ratio (M-H, Fixed, 95% CI)	1.84 [0.61, 5.53]
17.4 akathisia - medium-term	1	386	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.30, 5.82]
17.5 anxiety - short-term	2	461	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.52, 1.96]
17.6 anxiety - medium-term	1	386	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.41, 1.40]
17.7 delusions - medium-term	1	386	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.04, 0.80]
17.8 dizziness - short-term	1	121	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.21, 1.64]
17.9 fatigue - short-term	1	121	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.10, 2.76]
17.10 hallucinations - medium-term	1	386	Risk Ratio (M-H, Fixed, 95% CI)	0.08 [0.01, 0.58]
17.11 headache - short-term	2	461	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.22, 0.71]
17.12 headache - medium-term	1	386	Risk Ratio (M-H, Fixed, 95% CI)	2.97 [0.61, 14.53]
17.13 insomnia - short-term	2	461	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.50, 1.31]
17.14 insomnia - medium-term	1	386	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.24, 0.88]
17.15 nausea - short-term	1	121	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.62, 3.34]
17.16 oral hypoesthesia - short-term	1	340	Risk Ratio (M-H, Fixed, 95% CI)	1.89 [0.53, 6.74]
17.17 pain - short-term	1	121	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.18, 3.37]
17.18 psychosis - short-term	1	121	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.47, 5.31]
17.19 schizophrenia - medium-term	1	386	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.14, 0.59]
17.20 sedation - short-term	1	340	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.21, 2.18]
17.21 somnolence - short-term	2	461	Risk Ratio (M-H, Fixed, 95% CI)	1.88 [0.86, 4.08]
17.22 somnolence - medium-term	1	386	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.05, 5.41]
17.23 upper respiratory tract infection - short-term	1	121	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.33, 6.00]
17.24 worsening psychotic symptoms - short-term	1	340	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.21, 1.22]
18 Adverse effects: 5. Extrapyramidal symptoms - 5. 1 Incidence	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

18.1 any extrapyramidal symptoms - short-term	2	523	Risk Ratio (M-H, Fixed, 95% CI)	1.74 [1.02, 2.96]
18.2 any extrapyramidal symptoms - medium-term	1	386	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.24, 1.82]
18.3 dystonia - short-term	1	340	Risk Ratio (M-H, Fixed, 95% CI)	7.39 [0.42, 130.15]
18.4 hyperkinesia - short-term	1	121	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.5 hypertonia - short-term	1	121	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.28]
18.6 muscle rigidity - short-term	1	340	Risk Ratio (M-H, Fixed, 95% CI)	8.53 [0.49, 148.12]
18.7 Parkinsonism - short-term	1	340	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [0.61, 3.76]
18.8 Parkinsonism - medium-term	1	386	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 3.14]
19 Adverse effects: 5. Extrapyramidal symptoms - 5. 2. Average change (baseline-to-endpoint) (various scales, high= poor) - short-term	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
19.1 AIMS	1	333	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.43, 0.17]
19.2 BAS	1	333	Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.05, 0.27]
19.3 SAS	1	333	Mean Difference (IV, Fixed, 95% CI)	0.5 [-0.04, 1.04]
20 Adverse effects: 6. Incidence of death (for any reason) - short-term	2	523	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.02, 0.01]
21 Leaving the study early	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
21.1 any reason - short-term	5	1046	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.80, 1.04]
21.2 any reason - medium-term	1	386	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.38, 0.62]
21.3 due to adverse effects - short-term	3	644	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.54, 1.47]
21.4 due to adverse effects - medium-term	1	386	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.18, 0.50]
21.5 due to lack of efficacy - short-term	2	457	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.38, 0.81]
21.6 due to loss to follow up - medium-term	1	386	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.20, 4.84]
21.7 due to other reasons - short-term	2	457	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.83, 1.80]
21.8 due to other reasons - medium-term	1	386	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.38, 1.82]
21.9 due to relapse (not considered adverse effect) - medium-term	1	386	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.13, 0.49]
21.10 due to specific adverse effect: relapse - medium-term	1	386	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.16, 0.47]
21.11 due to specific adverse effect: worsening of schizophrenia - medium-term	1	386	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.14, 0.45]
21.12 due to withdrawal of consent - medium-term	1	386	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [0.78, 3.14]

ADDITIONAL TABLES

Table 1. Studies in this review which are relevant to others

Study	Comparison		Relevant existing Cochrane review
	adults	adolescents	
	with schizophrenia		
Chapel 2009; NCT00156065; NCT01142596; Kane 2010; NCT00156117; NCT01617187	Asenapine dose		None underway
NCT00156065; Kane 2010	Asenapine versus haloperidol		Kumar 2012
Cazorla 2008; NCT00151424; NCT00156117; NCT00156091; NCT01098110; NCT01617187	Asenapine versus olanzapine		Preda 2010
Chapel 2009	Asenapine versus quetiapine		
Potkin 2007	Asenapine versus risperidone		
NCT01190254		Asenapine dose	None underway
		Asenapine versus placebo	None underway
Kane 2010	Haloperidol versus placebo		Adams 2013
NCT00151424; NCT00156117; NCT00156091; NCT01098110; NCT01617187	Olanzapine versus placebo		Duggan 2005
Chapel 2009	Quetiapine versus placebo		Lankappa 2012
Potkin 2007	Risperidone versus placebo		Rattehalli 2010

CONTRIBUTIONS OF AUTHORS

Alistair Hay: Screening retrieved papers against eligibility criteria, extracting qualitative and quantitative data from papers, writing to authors of papers for additional information, providing additional data about papers (conversion of P values and SE to usable SD where appropriate, calculating average values for studies involving multiple asenapine arms), obtaining and screening of data from unpublished studies, entering qualitative and quantitative data into RevMan, analysis of data (summary of findings and meta-analyses), interpretation of data, providing a methodological perspective, writing the protocol/review (use of RevMan HAL software for results section, writing the abstract and discussion sections), liaison with Cochrane Schizophrenia Group (contact with Trials Search Coordinator for access to papers, and with course leader).

Amy Byers: Screening retrieved papers against eligibility criteria, appraising the quality of papers (identifying characteristics of studies and risks of bias), extracting qualitative and quantitative data from papers, entering qualitative data into RevMan, analysis of data (summary of findings), interpretation of data, providing a methodological perspective, writing the protocol/review (completing 'Characteristics of studies' tables and 'Risk of bias' tables, writing the abstract, results and discussion sections), liaison with Cochrane Schizophrenia Group (organised meetings with course leader).

Marco Sereno: Screening retrieved papers against eligibility criteria, identifying additional papers through handsearching, appraising the quality of papers (identifying characteristics of studies and risks of bias), providing additional data about papers (calculating average values for studies involving multiple asenapine arms), extracting qualitative and quantitative data from papers, obtaining and screening of data on unpublished studies, entering qualitative and quantitative data into RevMan, analysis of quantitative data (meta-analyses and summary of findings), interpretation of data, providing a methodological perspective, writing the protocol/review (writing the abstract, background and discussion sections).

Manpreet Basra: Screening retrieved papers against eligibility criteria, providing additional data about papers (identified all relevant scales in studies), entering data into RevMan, interpretation of data, providing a methodological perspective, writing the protocol/review (writing the abstract, results and discussion sections).

Snigdha Dutta: Screening retrieved papers against eligibility criteria, appraising quality of papers (identifying characteristics of studies and risks of bias), extracting qualitative data, entering qualitative data into RevMan, analysis of quantitative data (summary of findings), interpretation of data, providing a methodological perspective, writing the protocol/review (completing 'Characteristics of studies' tables and 'Risk of bias' tables and figures, writing the abstract, results and discussion sections).

Iram Jalil: see Acknowledgements.

DECLARATIONS OF INTEREST

Alistair Hay - none known.

Amy Byers - none known.

Marco Sereno - none known.

Manpreet Basra - none known.

Snigdha Dutta - none known.

SOURCES OF SUPPORT

Internal sources

- University of Nottingham, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

After seeking advice, we used the Mantel-Haenszel method to compute Risk Differences (RD) rather than Risk Ratio (RR) for binary outcomes in which at least one study had zero events in both asenapine and placebo trial arms. This included 1.12.1 QTc interval > 450ms and 1.21 Adverse effects: 6. Incidence of death.

INDEX TERMS

Medical Subject Headings (MeSH)

Antipsychotic Agents [adverse effects; *therapeutic use]; Heterocyclic Compounds, 4 or More Rings [adverse effects; *therapeutic use]; Psychotic Disorders [drug therapy]; Randomized Controlled Trials as Topic; Schizophrenia [*drug therapy]; Treatment Outcome

MeSH check words

Adult; Humans