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Bifeprunox versus placebo for schizophrenia (Review)

Chattopadhyay A, Frey S, Green G

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Bifeprunox versus placebo for schizophrenia (Review)

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	3
BACKGROUND	5
Figure 1.	6
OBJECTIVES	7
METHODS	7
RESULTS	12
Figure 2.	13
DISCUSSION	27
Figure 3.	30
Figure 4.	31
Figure 5.	32
AUTHORS' CONCLUSIONS	33
ACKNOWLEDGEMENTS	33
REFERENCES	34
CHARACTERISTICS OF STUDIES	39
DATA AND ANALYSES	48
Analysis 1.1. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 1 Global state: 1. Deteriorated.	60
Analysis 1.2. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 2 Global state: 2. Mean change (CGI-S, bigger negative value = good).	61
Analysis 1.3. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 3 Global state: 3. Mean endpoint score (CGI-I, lower = good).	61
Analysis 1.4. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 4 Mental state: 1. Mean change (PANSS total score, bigger negative value = good).	62
Analysis 1.5. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 5 Mental state: 3. Mean change (PANSS negative subscale, bigger negative value = good).	63
Analysis 1.6. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 6 Mental state: 2. Mean change (PANSS positive subscale, bigger negative value = good).	64
Analysis 1.7. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 7 Mental state: 4. Mean change (PANSS GPP subscale, bigger negative value = good).	64
Analysis 1.8. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 8 Mental state: 5. Mean change (BPRS total score, bigger negative value = good).	65
Analysis 1.9. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 9 Mental state: 6. Mean change (BPRS psychosis cluster, bigger negative value = good).	66
Analysis 1.10. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 10 Mental state: 7. Mean change (CDSS total score, bigger negative value = good).	66
Analysis 1.11. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 11 Leaving study early: 1. Total.	67
Analysis 1.12. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 12 Leaving study early: 2. Lack of efficacy.	67
Analysis 1.13. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 13 Leaving study early: 3. Adverse event.	68
Analysis 1.14. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 14 Leaving study early: 4. Loss to follow-up.	69
Analysis 1.15. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 15 Leaving study early: 5. Protocol violation.	70
Analysis 1.16. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 16 Leaving study early: 6. Withdrew consent.	71
Analysis 1.17. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 17 Leaving study early: 7. Other.	72
Analysis 1.18. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 18 Adverse effects: 1. Total.	73
Analysis 1.19. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 19 Adverse effects: 2. Gastrointestinal: i. Constipation. ..	74
Analysis 1.20. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 20 Adverse effects: 2. Gastrointestinal: ii. Dyspepsia.	74
Analysis 1.21. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 21 Adverse effects: 2. Gastrointestinal: iii. GI upset.	75
Analysis 1.22. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 22 Adverse effects: 2. Gastrointestinal: iv. Nausea.	76
Analysis 1.23. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 23 Adverse effects: 2. Gastrointestinal: v. Vomiting.	77
Analysis 1.24. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 24 Adverse effects: 2. Gastrointestinal: vi. Diarrhoea.	78

Analysis 1.25. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 25 Adverse effects: 3. Psychiatric: i. Anxiety.	78
Analysis 1.26. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 26 Adverse effects: 3. Psychiatric: ii. Psychosis aggravated.	79
Analysis 1.27. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 27 Adverse effects: 3. Psychiatric: iii. Schizophrenia aggravated.	80
Analysis 1.28. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 28 Adverse effects: 4. Extrapyramidal side effects: i. Extrapyramidal disorder.	80
Analysis 1.29. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 29 Adverse effects: 4. Extrapyramidal side effects: ii. Tremor.	81
Analysis 1.30. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 30 Adverse effects: 4. Extrapyramidal side effects: iii. Akathisia.	81
Analysis 1.31. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 31 Adverse effects: 4. Extrapyramidal side effects: iv. Bradykinesia.	82
Analysis 1.32. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 32 Adverse effects: 4. Extrapyramidal side effects: v. Chorea/athetosis.	83
Analysis 1.33. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 33 Adverse effects: 4. Extrapyramidal side effects: vi. Cogwheel rigidity.	83
Analysis 1.34. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 34 Adverse effects: 4. Extrapyramidal side effects: vii. Dyskinesia.	83
Analysis 1.35. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 35 Adverse effects: 4. Extrapyramidal side effects: viii. Dystonia.	84
Analysis 1.36. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 36 Adverse effects: 4. Extrapyramidal side effects: ix. Parkinsonism.	85
Analysis 1.37. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 37 Adverse effects: 4. Extrapyramidal side effects: x. Tardive dyskinesia.	85
Analysis 1.38. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 38 Adverse effects: 5. Lipid profile: i. Mean change (Total cholesterol, bigger negative value = good).	85
Analysis 1.39. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 39 Adverse effects: 5. Lipid profile: ii. Mean change (Triglycerides, bigger negative value = good).	86
Analysis 1.40. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 40 Adverse effects: 5. Lipid profile: iii. Mean change (VLDL, bigger negative value = good).	87
Analysis 1.41. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 41 Adverse effects: 5. Lipid profile: iv. Mean change (LDL, bigger negative value = good).	87
Analysis 1.42. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 42 Adverse effects: 5. Lipid profile: v. Mean change (HDL, bigger negative value = bad).	88
Analysis 1.43. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 43 Adverse effects: 5. Lipid profile: vi. TG:HDL ratio (bigger negative value = good).	88
Analysis 1.44. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 44 Adverse effects: 6. Weight: i. Mean change (kg, bigger positive value = bad).	88
Analysis 1.45. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 45 Adverse effects: 6. Weight: ii. Total number of participants with $\geq 7\%$ weight increase.	88
Analysis 1.46. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 46 Adverse effects: 6. Weight: iii. Total number of participants with $\geq 7\%$ weight decrease.	89
Analysis 1.47. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 47 Adverse effects: 6. Weight iv. Appetite decrease.	89
Analysis 1.48. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 48 Adverse effects: 6. Weight: v. Anorexia.	90
Analysis 1.49. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 49 Adverse effects: 7. Pain: i. General pain.	91
Analysis 1.50. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 50 Adverse effects: 7. Pain: ii. Back pain.	91
Analysis 1.51. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 51 Adverse effects: 7. Pain: iii. Arthralgia.	92
Analysis 1.52. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 52 Adverse effect: 8. Other: i. Asthenia.	92
Analysis 1.53. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 53 Adverse effects: 8. Other: ii. Dysmenorrhoea.	93
Analysis 1.54. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 54 Adverse effects: 8. Other: iii. Dry mouth.	93
Analysis 1.55. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 55 Adverse effects: 8. Other: iv. Fatigue.	94
Analysis 1.56. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 56 Adverse effects: 8. Other: v. Vaginitis.	94
Analysis 1.57. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 57 Adverse effects: 8. Other: vi. Dizziness.	95
Analysis 1.58. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 58 Adverse effects: 8. Other: vii. Somnolence.	95

Analysis 1.59. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 59 Adverse effects: 8. Other: viii. Sedation.	96
Analysis 1.60. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 60 Adverse effects: 8. Other: ix. Nasopharyngitis.	96
ADDITIONAL TABLES	96
CONTRIBUTIONS OF AUTHORS	98
DECLARATIONS OF INTEREST	99
SOURCES OF SUPPORT	99
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	99
INDEX TERMS	99

[Intervention Review]

Bifeprunox versus placebo for schizophrenia

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ABSTRACT

Background

Bifeprunox is a novel antipsychotic drug designed to treat schizophrenia. However, research into the drug was ceased in 2009 due to rejection of licence to go to market by the US Food and Drug Administration (FDA), who could not approve the drug for acute or long-term symptoms of schizophrenia because more research was required to demonstrate convincing effects "beyond those already achieved" with currently licenced drugs. There were also concerns expressed over one death of a person whilst on the drug.

Objectives

To investigate the clinical and adverse effects of bifeprunox for people with schizophrenia.

Search methods

We searched the Cochrane Schizophrenia Group's Trials Register on 23 October 2015, which is based on regular searches of MEDLINE, EMBASE, CINAHL, BIOSIS, AMED, PubMed, PsycINFO, and clinical trials registries. There are no language, date, document type, or publication status limitations for inclusion of records in the register.

Selection criteria

All randomised clinical trials focusing on bifeprunox versus placebo for schizophrenia.

Data collection and analysis

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

Main results

We included four randomised controlled trials (RCTs). We found evidence of missing data and poor reporting. When bifeprunox 20 mg was compared with placebo for schizophrenia, the drug resulted in a reduction of the Positive and Negative Syndrome Scale (PANSS) positive subscale score regarding positive symptoms ($n = 549$, 2 RCTs, MD -1.89 , 95% CI -2.85 to -0.92 , *low-quality evidence*) and the PANSS negative subscale regarding negative symptoms ($n = 549$, 2 RCTs, MD -1.53 , 95% CI -2.37 to -0.69 , *low-quality evidence*). There was a clear improvement regarding deterioration in the bifeprunox 20 mg group ($n = 231$, 1 RCT, RR 0.71 95% CI 0.54 to 0.93 , *very low-quality evidence*). The total number of participants with equal to or greater than 7% weight increase was similar between bifeprunox and placebo ($n = 483$, 1 RCT, RR 1.02 95% CI 0.31 to 3.33 *moderate-quality evidence*). There were no useable data for quality of life, economic outcomes, and service use.

Authors' conclusions

Our results showed some positive effects and a favourable adverse effect profile for bifeprunox, although there were few data overall and none were of high quality. It would seem that these data alone would not have been enough for the FDA to decide to halt progress of the drug to market. We can only assume that we are missing important data. Both the FDA and the relevant pharmaceutical companies have not made all relevant data accessible. As some of these trials also involved an additional haloperidol, olanzapine, quetiapine, or risperidone arm, these data are not only relevant to evaluation of bifeprunox. In not making all data accessible, it is hard to see how the FDA and the drug companies have fulfilled their full obligations to people with schizophrenia or their clinicians.

PLAIN LANGUAGE SUMMARY

Bifeprunox compared with placebo for schizophrenia

Review question

Is the antipsychotic bifeprunox an effective and safe treatment option for people with schizophrenia?

Background

Bifeprunox is an antipsychotic, developed to treat schizophrenia. It was thought to be effective for symptoms of schizophrenia whilst causing fewer of the side effects associated with other antipsychotics. However, in 2009 research into the drug was stopped, as it was considered to be no more effective than other available treatments, and there were concerns over the death of one person whilst on the drug.

However, as many people with schizophrenia are resistant to current treatments, there is a need to explore new options. Bifeprunox was one of these. We reviewed the available evidence for efficacy, safety, and side effects of bifeprunox, in part to aid in understanding why use of the drug was halted.

Searching for evidence

The Information Specialist of the Cochrane Schizophrenia Group searched the specialised register in October 2015. He ran an electronic search for trials that randomised people with schizophrenia to receive either bifeprunox or placebo, finding 42 records. The review authors screened these for inclusion in the review.

Evidence found

Only four trials provided useable data, and these were of poor quality with some evidence of missing data. Two trials are completed but not yet published; we could not obtain any information from these trials that we could use in this review. The data available to us showed that bifeprunox improved participants' scores on both positive and negative symptom scales. Weight increase was similar between those receiving bifeprunox and those allocated to placebo.

Conclusions

Data regarding the effects of bifeprunox are scarce. The data we found, which were of poor quality, showed no real evidence that bifeprunox is unsafe or ineffective. Its effects do not seem significantly different to other drugs that are currently on the market. More data on this compound exists but is not publicly available. We believe that the licencing authority in the USA must have had more information on which to base their important decision. The drug company also seemed to lose the will to move forward with bifeprunox. Whether or not the decision to prohibit access to a potentially useful drug was taken because of clear evidence of adverse effects, market calculations, or biases, it would seem an omission that all information upon which this decision was made is not in the public domain.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. BIFEPRUNOX versus PLACEBO for schizophrenia

BIFEPRUNOX versus PLACEBO for schizophrenia

Patient or population: People with schizophrenia

Settings:

Intervention: Bifeprunox 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	Bifeprunox versus placebo				
Mental state: 1. Mean change PANSS positive subscale (lower value = good)		Mental state: 1. Mean change in score for the intervention group was 1.89 lower (2.85 to 0.92 lower)		549 (2 studies)	⊕⊕⊕⊕ low ^{1,2}	
Mental state: 2. Mean change PANSS negative subscale (lower value = good)		Mental state: 2. Mean change in score for the intervention group was 1.53 lower (2.37 to 0.69 lower)		549 (2 studies)	⊕⊕⊕⊕ low ^{1,2}	
Service use: Re-admission	See comment	See comment	Not estimable	0 (0)	See comment	No trial reported this outcome
Global state: Deteriorated CGI Follow-up: 6 months	600 per 1000	426 per 1000 (324 to 558)	RR 0.71 (0.54 to 0.93)	231 (1 study)	⊕⊕⊕⊕ very low ^{4,5,6}	moderate ³
Quality of life: Important change	See comment	See comment	Not estimable	0 (0)	See comment	No trial reported this outcome
Adverse effects: Weight - Total number of participants with ≥ 7% weight increase	25 per 1000	25 per 1000 (24 to 25)	RR 1.02 (0.31 to 3.33)	483 (1 study)	⊕⊕⊕⊕ moderate ¹	

Economics: Cost	See comment	See comment	Not estimable	0 (0)	See comment	No trial reported this outcome
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*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).

CGI: Clinical Global Impression; **CI:** Confidence interval; **PANSS:** Positive and Negative Syndrome Scale; **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.

¹Risk of bias: rated 'serious' - poor reporting of methods, funded by industry.

²Indirectness: rated 'serious' - no trial reported 'clinically important difference' as pretested as key outcome for this table.

³Moderate control risk - rounded to 60% from that within the trial.

⁴Risk of bias: rated 'very serious' - no description of randomisation, blinding, selective reporting, funded by industry, and no response when authors contacted.

⁵Indirectness: rated 'serious' - deterioration proxy for 'relapse'.

⁶Publication bias: rated 'detected' - authors written to regarding clarification from abstract and no reply.

BACKGROUND

Description of the condition

Schizophrenia is a severe, debilitating, and often chronic psychotic disorder that is characterised by positive symptoms (lack of insight, delusions, thought disorder, and hallucinations), negative symptoms (such as avolition and diminished emotional expression), and disorganisation (Diagnostic and Statistical Manual of Mental Disorders (DSM-V) ([American Psychiatric Association 2013](#))). It currently affects about 21 million people worldwide ([WHO 2014](#)), 0.3% to 0.7% of the world's population at some point in their lives ([van Os 2009](#)). Genetic and environmental factors can influence the development of schizophrenia. Having a parent with the condition increases the risk to 13%, whilst having both parents with the condition increases the risk to almost 50% ([Hersen 2011](#)). People born in urban areas are more likely to develop the condition ([Pedersen 2001](#)), as are those who use cannabis ([Arseneault 2004](#)).

Whilst one-third of those diagnosed with schizophrenia fully recover, others suffer from an unremitting illness consisting of long periods of substantial recovery from the positive symptoms ([Ratthahalli 2010](#)). Life expectancy in people with schizophrenia can fall by up to 20%; suicide risk increases, as does the risk of coronary heart disease ([Hennekens 2005](#)). Individuals are also likely to have other psychiatric comorbidities, such as panic disorder and depression ([Buckley 2009](#)).

Schizophrenia not only impacts severely on the lives of those who suffer from the illness and their relatives, it is extremely costly to the wider community ([McDonnell 2003](#); [Rupp 1993](#)). In the UK, for instance, the total annual cost to society of managing schizophrenia and its related effects is estimated at GBP 11.8 billion ([Andrew 2012](#)). This is a huge economic burden to society and highlights the importance of research into the treatment of schizophrenia that might reduce this burden. Amidst a wide range of both pharmacological and psychological treatment options, antipsychotics have been, and remain, the main treatment option.

Description of the intervention

In the 1950s conventional antipsychotic (or first-generation antipsychotic) drugs became more widely used as a drug treatment for schizophrenia ([Lehmann 1997](#)). Typical antipsychotics, such as chlorpromazine, block dopamine receptors and were shown to alleviate the positive symptoms associated with schizophrenia ([Dixon 1995](#)). However, these drugs were not as effective as anticipated ([Ratthahalli 2010](#)). Although the drugs alleviate positive

symptoms, they are not effective for negative symptoms, and so do not always result in a complete recovery. Their mechanism of action can lead to severe side effects such as akathisia, parkinsonism, and tardive dyskinesia ([Gerlach 2002](#)).

As a result, there was an increased interest in alternative atypical (or second-generation) antipsychotic medication, such as risperidone and olanzapine. These drugs are antagonists for serotonin and dopamine receptors and are associated with reduced risk of severe movement disorders ([Hoiberg 2006](#); [Tandon 2008](#)). However, adverse metabolic outcomes can occur, such as severe weight gain, insulin resistance, and diabetes ([Meyer 2004](#); [Newcomer 2006](#); [Tandon 2008](#)).

The choice of a particular drug, or class of drugs, is principally influenced by the efficacy as well as the safety properties of the drug ([Jauhar 2012](#)), therefore further increasing interest in alternative medications. Third-generation antipsychotic medication emerged to deliver a treatment with both fewer negative symptoms and fewer metabolic side effects. Drugs such as aripiprazole and bifeprunox are examples of these third-generation antipsychotics. [Casey 2008a](#) highlighted the efficacy of bifeprunox over placebo treatment in controlling the symptoms of schizophrenia and in causing fewer metabolic problems. Despite this promising efficacy profile, it did not gain regulatory approval and was rejected by the US Food and Drug Administration (FDA; [Newman-Tancredi 2010](#)).

How the intervention might work

As a novel atypical antipsychotic drug, bifeprunox ([Figure 1](#)) has a high affinity for both serotonin 5-HT_{1A} receptors and dopamine D₂ receptors and acts as a partial agonist on these receptors ([Newman-Tancredi 2005](#)). Bifeprunox has also been found to have a greater intrinsic efficacy upon D₂/D₃ dopamine receptors than other atypical antipsychotics such as aripiprazole ([Tadori 2007](#)). Bifeprunox can act as a dopamine system stabiliser, meaning it can increase dopamine levels where they are low and decrease them where they are too high. This could explain why it is effective at reducing both positive and negative symptoms ([Stahl 2002](#)). While the majority of atypical antipsychotic treatments for schizophrenia, such as clozapine and olanzapine, have been associated with weight gain ([Haddad 2005](#)), bifeprunox treatment was associated with weight loss and favourable effects on total cholesterol and triglyceride levels in a short-term clinical trial at 20 mg ([Casey 2008a](#)). However, certain adverse side effects have also been linked to bifeprunox treatment, such as nausea, dyspepsia, vomiting, and constipation ([Barbato 2006a](#)).

Figure 1. Bifeprunox structure.

Why it is important to do this review

The mechanism of action of bifeprunox has the potential to offer a more beneficial treatment in terms of its efficacy in reducing the symptoms of schizophrenia, but also in reducing some of the side effects. In addition, preliminary evidence of these beneficial effects has been found (Casey 2008a). Reviewing bifeprunox could therefore indicate whether further investigation into the drug is worthwhile. Exploring the efficacy and effectiveness of third-generation drugs is vital for the improvement of schizophrenia treatment, as patients' quality of life is severely affected, and some people remain resistant to the current treatment options (Jones 2006; Valenstein 2004). The exploration of bifeprunox is particularly

relevant as it has been shown to demonstrate a decrease in weight, as opposed to the well-documented and negative side effect of weight gain with second-generation antipsychotics (Casey 2008a).

Furthermore, the FDA has acknowledged some efficacy of bifeprunox, yet did not approve the drug for acute or long-term symptoms of schizophrenia, stating that more research was required to demonstrate convincing effects beyond those already achieved with currently licenced drugs (Jeffrey 2007; Ye 2014). However, it is conceivable that the drug offers equally effective treatment; symptoms of schizophrenia are reduced, whilst preserving a better quality of life for the person by reducing the problematic side effects associated with both typical and atypical

antipsychotics. Research of the drug was halted in 2009 after the FDA judgement in 2007, and therefore some confusion remains over whether there was any feasible potential and future for bifeprunox. This review looked at the efficacy, safety, and side effects of bifeprunox with the goal of providing clarity on whether the halt on drug development was appropriate.

OBJECTIVES

To investigate the clinical and adverse effects of bifeprunox for people with schizophrenia.

If possible, to undertake several subgroup analyses within this review (see [Subgroup analysis and investigation of heterogeneity](#)).

METHODS

Criteria for considering studies for this review

Types of studies

All relevant randomised controlled trials. If a trial was described as 'double-blind' but had implied randomisation, we would have included such trials in a sensitivity analysis (see [Sensitivity analysis](#)). If we found quasi-randomised studies, such as those allocating by alternate days of the week, we would have excluded them. Where people were given additional treatments within the bifeprunox group, we would only include data if the adjunct treatment was evenly distributed between groups, and it was only the bifeprunox that was randomised.

Types of participants

Adults aged 18 to 65 years old with schizophrenia or related disorders, including schizophreniform disorder, schizoaffective disorder, and delusional disorder, again by any means of diagnosis. However, we excluded trials if more than 20% of the sample was over 65 years old. We only included trials where the majority of participants (more than 50%) had schizophrenia.

We were interested in ensuring that information was as relevant to the current care of people with schizophrenia as possible, so if information was provided, we proposed to clearly highlight the current clinical state (acute, early postacute, 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. Bifeprunox

Any dose or mode of administration.

2. Placebo

Active or inactive or no treatment.

Types of outcome measures

We planned to divide all outcomes into short term (zero to six weeks), medium term (six weeks to six months), and long term (over six months).

Primary outcomes

1. Global state

- 1.1 Relapse - as defined by individual studies
- 1.2 Clinically important improvement - as defined by individual studies

2. Service use

- 2.1 Hospitalisation - mean number of days per month in hospital

3. Mental state

- 3.1 Specific symptoms
 - 3.1.1 Positive symptoms - clinically important improvement - as defined by individual studies
 - 3.1.2 Negative symptoms - clinically important improvement - as defined by individual studies

4. Adverse effects

- 4.1 Specific - important adverse effects

Secondary outcomes

1. Global state

- 1.1 Severity of illness (binary or continuous measures)

2. Service use

- 2.1 Duration of hospital stay
- 2.2 Re-admission
- 2.3 Contact with psychiatric services (binary or continuous measures)

3. Mental state

- 3.1 General symptoms - any change (binary or continuous measures)
- 3.2 Specific symptoms - any change (binary or continuous measures)
 - 3.2.1 Positive symptoms (delusions, hallucinations, disordered thinking)
 - 3.2.2 Negative symptoms (avolition, poor self care, blunted affect)
 - 3.2.3 Mood - depression

4. Leaving the study early

- 4.1 Rate of leaving
- 4.2 Reasons for leaving early

5. Behaviour

- 5.1 General behaviour (binary or continuous measures)
- 5.2 Occurrence of violent incidents (to self, others, or property)
- 5.3 Social functioning (binary or continuous measures - examples given)
 - 4.3.1 Imprisonment (police contact and arrest)
 - 4.3.2 Employment status (employed/unemployed)
 - 4.3.3 Accommodation status
 - 4.3.4 Alcohol use
 - 4.3.5 Illicit drug use

6. Quality of life

- 6.1 Clinically important change - as defined by individual studies
- 6.1 Participant satisfaction (binary or continuous measures)
- 6.2 Carer's satisfaction (binary or continuous measures)

7. Adverse effects

- 7.1 General (binary or continuous measures)
- 7.2 Specific (binary or continuous measures - examples given)
 - 7.2.1 Weight change
 - 7.2.2 Anticholinergic effects - dry mouth
 - 7.2.3 Anticholinergic effects - sedation
 - 7.2.4 Extrapyrimal effects - movement disorders (e.g. tardive dyskinesia)

8. Economic

- 8.1 Direct costs
- 8.2 Indirect costs
- 8.3 Cost-effectiveness

'Summary of findings' table

We used the GRADE approach to interpret findings ([Schünemann 2008](#)), and used GRADE profiler ([GRADEPRO](#)) to import data from RevMan 5 ([Review Manager](#)) to create 'Summary of findings for the main comparison'. These tables provided outcome-specific information concerning the overall quality of evidence from each included study in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on all outcomes we rated as important to patient care and decision-making. We aimed to select the following main outcomes for inclusion in the [Summary of findings for the main comparison](#).

1. Global state - relapse - as defined by individual studies (medium term)
2. Service use - hospitalisation (medium term)
3. Mental state - positive symptoms - clinically important change (medium term)
4. Mental state - negative symptoms - clinically important change (medium term)
5. Quality of life - clinically important change (medium term)
6. Adverse effects - important degrees of weight gain (medium term)
7. Cost (medium term)

Search methods for identification of studies

Electronic searches

Cochrane Schizophrenia Group's Trials Register

The Trials Search Co-ordinator searched the Cochrane Schizophrenia Group's Study-Based Register of Trials using the following search strategy:

(*Bifeprunox* AND *Placebo*) in Intervention of STUDY

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

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

Searching other resources

1. Reference searching

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

2. Personal contact

We contacted the first author of each included study for information regarding unpublished trials. We noted the outcome of this contact in the included or awaiting assessment studies tables.

Data collection and analysis

Selection of studies

Review authors SF, GG, AH, AM, and AY independently inspected citations from the searches and identified relevant abstracts. Where disputes arose, we acquired the full report for more detailed scrutiny. SF, GG, AH, AM, and AY obtained and inspected the full reports of the abstracts meeting the review criteria. Review author AC repeated this whole process a few months later to ensure reliability. Where 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 SF, GG, AH, AM, and AY initially extracted data from all included studies. In addition, to ensure reliability, the same review authors independently extracted data from a random sample of these studies comprising 10% of the total. Disagreements were discussed, decisions documented, and, if necessary, authors of studies contacted for clarification. Review author AC then extracted data once again to improve reliability. We attempted to extract data presented only in graphs and figures whenever possible, but only included such data if two review authors independently reached the same result. We attempted to contact authors through an open-ended request in order to obtain missing information or for clarification whenever necessary. If studies were multicentre, where possible, we extracted data relevant to each component centre separately.

2. Management

2.1 Forms

We extracted data onto standard, simple forms.

2.2 Scale-derived data

We included continuous data from rating scales only if:

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

Ideally, the measuring instrument should have been either be i. a self report or ii. completed by an independent rater or relative (not the therapist). We realise that this was not often reported clearly; in [Description of studies](#) we noted whether or not this was the case.

2.3 Endpoint versus change data

Both endpoint and change data have advantages. Change data can remove a component of between-person variability from the analysis. On the other hand, calculation of change needs two assessments (baseline and endpoint), which can be difficult in unstable and hard-to-measure conditions such as schizophrenia. We decided to primarily use endpoint data, only using change data if the former were not available. We combined endpoint and change data in the analysis, as we preferred to use mean differences rather than standardised mean differences throughout (Higgins 2011).

2.4 Skewed data

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

(Note that we entered data from studies of at least 200 participants in the analysis irrespective of the following rules, because skewed data pose less of a problem in large studies. The rules below are what we would have done had we found trials including less than 200 participants. We also entered change data, as when continuous data are presented on a scale that includes a possibility of negative values (such as change data), it is difficult to tell whether data are skewed or not. We presented and entered change data into statistical analyses.)

For endpoint data, $N < 200$:

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

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

2.5 Common measure

To facilitate comparison between trials, we planned to convert 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 (for example mean days per month).

2.6 Conversion of continuous to binary

We planned to make efforts to convert outcome measures to dichotomous data. We did this by identifying cutoff 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), in Overall 1962, or the PANSS, in Kay 1986, this could be considered to be a clinically significant response (Leucht 2005; Leucht 2005a). If data based on these

thresholds were not available, we planned to use the primary cutoff presented by the original authors.

2.7 Direction of graphs

Where possible, we entered data in such a way that the area to the left of the line of no effect indicated a favourable outcome for bifeprunox. Where keeping to this made it impossible to avoid outcome titles with clumsy double-negatives (for example 'not unimproved'), we reported data where the left of the line indicated an unfavourable outcome. We noted this in the relevant graphs.

Assessment of risk of bias in included studies

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

If the raters disagreed, we made the final rating by consensus. Where inadequate details of randomisation and other characteristics of trials were provided, we attempted to contact the authors of the studies in order to obtain further information. We reported non-concurrence in quality assessment. If disputes arose as to which category a trial was to be allocated, we again resolved this 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 ratio (Boissel 1999), and that clinicians tend to interpret odds ratios as RR (Deeks 2000).

2. Continuous data

For continuous outcomes we estimated the mean difference between groups. We preferred not to calculate effect size measures (standardised mean difference). However, if scales of very considerable similarity were used, we would presume there was a small difference in measurement, and calculate effect size and transform 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 pose problems. Firstly, authors often fail to account for intraclass 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). If we encountered cluster trials in our analyses, we would have taken the following steps.

Where clustering was not accounted for in primary studies, we would have presented the data in a table with a (*) symbol to indicate the presence of a probable unit of analysis error, and contacted first authors of studies to obtain intraclass correlation coefficients for their clustered data, and to adjust for this by using accepted methods (Gulliford 1999). Where clustering had been incorporated into the analysis of primary studies, we would have presented these data as if from a non-cluster-randomised study, but adjusted for the clustering effect.

We have sought statistical advice and been advised that the binary data as presented in a report should be divided by a 'design effect'. This is calculated using the mean number of participants per cluster (m) and the intraclass correlation coefficient (ICC) (Design effect = $1 + (m - 1) \times \text{ICC}$) (Donner 2002). If the ICC was not reported, we would have assumed it to be 0.1 (Ukoumunne 1999).

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

2. Cross-over trials

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

3. Studies with multiple treatment groups

Where a study involved more than two treatment arms, we planned to present the additional treatment arms in comparisons if they were relevant. If data were binary, we would simply add these and combine them within the two-by-two table. If data were continuous, we would combine data following the formula in Section 7.7.3.8 (Combining groups) of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Where the additional treatment arms were not relevant, we would not reproduce these data.

Dealing with missing data

1. Overall loss of credibility

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

2. Binary

Where attrition for a binary outcome was between 0% and 50%, and where these data were not clearly described, we presented

data on a 'once-randomised-always-analyse' basis (an intention-to-treat analysis). We assumed that all participants leaving the study early had the same rates of negative outcome as those who completed, with the exception of the outcome of death and adverse effects. For these outcomes we used the rate of those who stayed in the study - in that particular arm of the trial - for those who did not. If the above criteria had been met, we would have undertaken a sensitivity analysis to test how prone the primary outcomes were to change when data only from people who completed the study to that point were compared to the intention-to-treat analysis using the above assumptions. However, in this review the data regarding attrition were clearly described, so there was no need for a sensitivity analysis.

3. Continuous

3.1 Attrition

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

3.2 Standard deviations

If SDs were not reported, we first tried to obtain the missing values from the authors. If not available, where measures of variance for continuous data were missing, but an exact standard error (SE) and confidence intervals were available for group means, and either a P value or t value were available for differences in mean, we calculated SDs according to the rules described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). When only the SE was reported, we calculated SDs by the formula $\text{SD} = \text{SE} \times \text{square root } (n)$. Sections 7.7.3 and 16.1.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* present detailed formulas for estimating SDs from P values, t or F values, confidence intervals, ranges, or other statistics (Higgins 2011). If these formulas did not apply, we would have 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. Should this technique have been necessary to employ, we would have examined the validity of the imputations in a sensitivity analysis excluding imputed values.

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

Various methods are available to account for participants who left the trials early or were lost to follow-up. Some trials 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 of a standard. While the latter methods seem to be somewhat better than LOCF (Leon 2006), we felt that the high percentage of participants leaving the studies early and differences in reasons for leaving the studies early between groups is often the core problem in randomised schizophrenia trials (Leucht 2007). We therefore did not exclude studies based on the statistical approach used. However, we did prefer use of the more sophisticated approaches. For example, we preferred MMRM or multiple imputation to LOCF, and we only presented completer analyses if some kind of intention-to-treat data was not available at all. Moreover, we addressed this issue in the 'incomplete outcome data' domain of the 'Risk of bias' tool.

Assessment of heterogeneity

1. Clinical heterogeneity

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

2. Methodological heterogeneity

We considered all included studies initially, without seeing comparison data, to judge methodological heterogeneity. We simply inspected all studies for clearly outlying methods that we had not predicted would arise. When such methodological outliers arose, we fully discussed them.

3. Statistical heterogeneity

3.1 Visual inspection

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

3.2 Employing the I^2 statistic

We investigated heterogeneity between studies by considering the I^2 statistic alongside the χ^2 P value. The I^2 statistic provided an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of I^2 depended on i. the magnitude and direction of effects and ii. the strength of evidence for heterogeneity (for example a P value from the χ^2 test or a confidence interval for I^2). We interpreted an I^2 estimate greater than or equal to around 50%, accompanied by a statistically significant χ^2 test, as evidence of substantial levels of heterogeneity (Section 9.5.2; Higgins 2011). When we found substantial levels of heterogeneity in the primary outcome, we explored the reasons for heterogeneity (Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). These are described in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We were aware that funnel plots might have been useful in investigating reporting biases but were of limited power to detect small-study effects. We did not use funnel plots for outcomes where there were 10 or fewer studies, or where all studies were of similar size. If funnel plots had been possible, we would have sought statistical advice in their interpretation.

Data synthesis

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

effect, these studies can either inflate or deflate the effect size. We chose a random-effects model for all analyses.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

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

We also attempted to undertake subgroup analyses to compare the results for the following: high dose (more than 21 mg per day) versus medium dose (11 to 20 mg per day) versus low dose (0 to 10 mg per day).

2. Investigation of heterogeneity

We reported whether inconsistency was high. First we investigated whether data had been entered correctly. Second, if the data were correct, we visually inspected the graph and successively removed studies outside of the company of the rest to see if homogeneity was restored. For this review we decided that when this occurred with data contributing to the summary finding of no more than around 10% of the total weighting, we presented the data. If not, we did not pool the data and we discussed the issues. We know of no supporting research for this 10% cutoff, but we are investigating the use of prediction intervals as an alternative to this unsatisfactory state.

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

Sensitivity analysis

1. Implication of randomisation

If we had found trials that implied randomisation, we would have completed a sensitivity analysis for the primary outcome. If inclusion of their data did not result in a substantive difference, we would have kept them in the analyses. If their inclusion did result in statistically significant differences, we would not add the data from these lower-quality studies to the results of the better trials, but presented such data within a subcategory.

2. Assumptions for lost binary data

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

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

3. Risk of bias

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

4. Imputed values

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

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

5. Fixed-effect and random-effects

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

RESULTS

Description of studies

See [Characteristics of included studies](#) and [Characteristics of excluded studies](#).

Results of the search

The original searches in 2015 yielded 42 records; after initial inspection we selected 29 records for further inspection. We were able to include four studies in the final review (see [Figure 2](#)). Two completed studies are awaiting publication, which, because the licence for the drug was not granted, may never be published ([NCT00139906](#); [NCT00139919](#)).

Figure 2. Study flow diagram.

Included studies

We included four studies.

1. Methods

All four trials were of parallel design and randomised ([Barbato 2006](#); [Bourin 2007](#); [Casey 2007](#); [Meltzer 2007](#)).

2. Length of trials

Three trials were of six weeks duration ([Barbato 2006](#); [Casey 2007](#); [Meltzer 2007](#)). One study consisted of both six-month and six-week trials ([Bourin 2007](#)).

3. Participants

Participants in all trials were reported to have schizophrenia. All trials used the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) diagnostic criteria. A total of 2289 participants are now included in this review.

4. Setting

[Bourin 2007](#) and [Casey 2007](#) took place in hospital. The other two studies did not report on setting ([Barbato 2006](#); [Meltzer 2007](#)).

[Meltzer 2007](#) was carried out in the USA and [Casey 2007](#) in the USA and Canada; the other two studies did not report on country ([Barbato 2006](#); [Bourin 2007](#)).

5. Study size

The mean number of participants was 572, ranging from 497 in [Bourin 2007](#) to 604 in [Barbato 2006](#).

6. Interventions

6.1 Bifepunox

The doses of bifepunox ranged from 5 mg per day in [Casey 2007](#) to 40 mg per day in [Meltzer 2007](#). The most common doses were 20 mg and 30 mg, featuring in three trials each.

6.2 Placebo

All trials compared bifepunox with placebo. No further details were given about the placebo.

6.3 Other drug treatment arms

Three of the trials included at least one more drug treatment arm in addition to placebo and bifepunox. We did not include data from these treatment arms, however they might be relevant for other reviews (see [Table 1](#)).

7. Outcomes

The included studies reported the following outcomes: global state, mental state, leaving study early, and adverse effects. Most outcomes were reported as continuous measures from scale-derived data.

7.1 Outcome scales

The following scales provided continuous data for the analysis.

7.1.1 Global state

i. Clinical Global Impression (CGI) ([Guy 1976](#)). A rating instrument commonly used in studies on schizophrenia that enables clinicians to quantify severity of illness and overall clinical improvement. A seven-point scoring system is usually used, with low scores

indicating decreased severity or greater recovery, or both. Three studies used this scale ([Bourin 2007](#); [Casey 2007](#); [Meltzer 2007](#)).

7.1.2 Mental state

i. Positive and Negative Syndrome Scale (PANSS) ([Kay 1987](#)). This scale assesses the severity of psychotic symptomatology in general. It consists of three subscales, positive symptoms, negative symptoms, and general psychopathology, and a total score. Three studies used this scale ([Bourin 2007](#); [Casey 2007](#); [Meltzer 2007](#)).

ii. Brief Psychiatric Rating Scale (BPRS) ([Lukoff 1996](#)). This is a semi-structured interview that assesses the major psychiatric symptoms. It is a 16-item scale, with each item scored on a seven-point scale, ranging from 'not present' to 'extremely severe'. The range of possible scores is 24 to 168; high scores indicate more severe symptoms. [Bourin 2007](#) and [Casey 2007](#) reported data from the BPRS.

iii. Calgary Depression Scale for Schizophrenia (CDSS) ([Addington 1993](#)). This nine-item structured interview scale was developed specifically for assessing depression in individuals with schizophrenia. The CDSS assesses depression as separate from overlapping negative or extrapyramidal symptoms. Higher scores indicate greater depression. [Bourin 2007](#) used this scale.

7.2 Missing outcomes

None of the studies reported the primary outcome hospitalisation or the global secondary outcomes re-admission, contact with psychiatric services, and severity of illness, and no study attempted to quantify quality of life or cost.

In one of the reports of the [Bourin 2007](#) trial, [Shapira 2007b](#), we identified one table (Table 6 of the report) reporting a six-week study that seemed not to be any of those we have already included. We have not included these limited data as we do not know the parent study.

Excluded studies

We excluded three studies because of lack of data (see [Characteristics of excluded studies](#)). Our attempts to contact authors and companies to get further data were unsuccessful. It seems likely that these data do exist, and so we hope that one day these will be made available.

Awaiting assessment

No studies are currently awaiting assessment.

Ongoing studies

Two records found in the literature search stated that their research had been completed, yet there were no available data. We emailed Solvay in October and November 2015 and were informed that Solvay had sold its pharmaceutical division in 2009. It seems unlikely that these data will ever be published. We are unsure if these trials differ from the ones we have either included or excluded.

Risk of bias in included studies

See also 'Risk of bias' tables in [Characteristics of included studies](#).

Allocation

All studies were randomised trials, however most did not provide explicit details of the method of randomisation or allocation concealment. We rated these as at 'unclear' risk of bias.

Blinding

Most studies claimed to use a double-blind technique, however, again, they did not provide explicit details of the methods used and were therefore again rated as at 'unclear' risk of bias.

Incomplete outcome data

We rated all four studies as at 'low' risk of bias for incomplete outcome data, with most studies clearly reporting reasons for leaving the trial.

Selective reporting

We rated [Bourin 2007](#) as at 'low' risk of bias with regard to selective reporting. We rated two other studies as at 'unclear' risk ([Casey 2007](#); [Meltzer 2007](#)), as all outcomes were reported but some means or SDs were omitted. We rated the remaining study as at 'high' risk of bias with regard to selective reporting, as not all outcomes were reported ([Barbato 2006](#)).

Other potential sources of bias

We rated all studies as at 'high' risk, as all were funded by the 'interested' industry.

Effects of interventions

See: [Summary of findings for the main comparison BIFEPRUNOX versus PLACEBO for schizophrenia](#)

For this review we generated a single comparison. We were able to extract numerical data from four randomised studies.

1. COMPARISON 1: BIFEPRUNOX versus PLACEBO

This comparison has 60 outcomes, which was an unfortunate result of several of the studies being essentially dose-ranging studies, so each dose was compared with placebo and reports presented separately. We decided to keep the doses separate in this report.

1.1 Global state: 1. Deteriorated

1.1.1 20 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 231 participants. For this outcome, within this subgroup, we found evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (risk ratio (RR) 0.71, 95% confidence interval (CI) 0.54 to 0.93; [Analysis 1.1](#)).

1.1.2 30 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 241 participants. We found evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 0.61, 95% CI 0.46 to 0.81; [Analysis 1.1](#)).

1.2 Global state: 2. Mean change (CGI-S, bigger negative value = good)

We found three studies relevant to this outcome and divided the data into five subgroups in accordance with our protocol.

1.2.1 5 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 224 participants. For this outcome, within this subgroup, we found evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (mean difference (MD) -0.33, 95% CI -0.59 to -0.07; [Analysis 1.2](#)).

1.2.2 10 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 232 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (MD 0.07, 95% CI -0.17 to 0.31; [Analysis 1.2](#)).

1.2.3 20 mg bifeprunox

We found two trials to be relevant to this subgroup with a total of 549 participants. We found evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (MD -0.28, 95% CI -0.47 to -0.1; [Analysis 1.2](#)).

1.2.4 30 mg bifeprunox

We found two trials to be relevant to this subgroup with a total of 622 participants. We found evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (MD -0.25, 95% CI -0.44 to -0.06; [Analysis 1.2](#)).

1.2.5 40 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 285 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (MD -0.1, 95% CI -0.36 to 0.16; [Analysis 1.2](#)).

1.3 Global state: 3. Mean endpoint score (CGI-I, lower = good)

We identified two studies relevant to this outcome and categorised data into four subgroups (in keeping with our protocol).

1.3.1 5 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 224 participants. For this outcome, within this subgroup, we found no evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (MD -0.28, 95% CI -0.64 to 0.08; [Analysis 1.3](#)).

1.3.2 10 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 232 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (MD 0.29, 95% CI -0.07 to 0.65; [Analysis 1.3](#)).

1.3.3 20 mg bifeprunox

We found two trials to be relevant to this subgroup with a total of 549 participants. We found evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (MD -0.41, 95% CI -0.81 to -0.01). This subgroup had important levels of heterogeneity ($\text{Chi}^2 = 3.19$; $\text{df} = 1.0$; $P = 0.07$; $I^2 = 68\%$; [Analysis 1.3](#)).

1.3.4 30 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 338 participants. For this outcome, within this subgroup, we found

evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (MD -0.6, 95% CI -0.88 to -0.32; [Analysis 1.3](#)).

1.4 Mental state: 1. Mean change (PANSS total score, bigger negative value = good)

We found two studies relevant to this outcome and divided the data into four subgroups in accordance with our protocol.

1.4.1 5 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 224 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (MD -4.4, 95% CI -8.83 to 0.03; [Analysis 1.4](#)).

1.4.2 10 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 232 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (MD 0.3, 95% CI -4.16 to 4.76; [Analysis 1.4](#)).

1.4.3 20 mg bifeprunox

We found two trials to be relevant to this subgroup with a total of 549 participants. For this outcome, within this subgroup, we found evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (MD -7.03, 95% CI -9.98 to -4.07; [Analysis 1.4](#)).

1.4.4 30 mg bifeprunox

There is a single trial in this subgroup, with a total of 338 people. We found evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (MD -7.5, 95% CI -11.38 to -3.62; [Analysis 1.4](#)).

1.5 Mental state: 2. Mean change (PANSS positive subscale, bigger negative value = good)

We found three studies relevant to this outcome and divided the data into five subgroups in accordance with our protocol.

1.5.1 5 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 224 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (MD -1.2, 95% CI -2.56 to 0.16; [Analysis 1.6](#)).

1.5.2 10 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 232 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (MD 0.6, 95% CI -0.86 to 2.06; [Analysis 1.6](#)).

1.5.3 20 mg bifeprunox

We found two trials to be relevant to this subgroup with a total of 549 participants. We found evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (MD -1.89, 95% CI -2.85 to -0.92; [Analysis 1.6](#)).

1.5.4 30 mg bifeprunox

We found two trials to be relevant to this subgroup with a total of 622 participants. For this outcome, within this subgroup, we found evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (MD -2.18, 95% CI -3.26 to -1.1; [Analysis 1.6](#)).

1.5.5 40 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 285 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (MD -1.7, 95% CI -3.43 to 0.03; [Analysis 1.6](#)).

1.6 Mental state: 3. Mean change (PANSS negative subscale, bigger negative value = good)

We identified three studies relevant to this outcome and categorised data into five subgroups (in keeping with our protocol).

1.6.1 5 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 224 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (MD -0.9, 95% CI -2.15 to 0.35; [Analysis 1.5](#)).

1.6.2 10 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 232 participants. For this outcome, within this subgroup, we found no evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (MD -0.4, 95% CI -1.6 to 0.8; [Analysis 1.5](#)).

1.6.3 20 mg bifeprunox

We found two trials to be relevant to this subgroup with a total of 549 participants. We found evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (MD -1.53, 95% CI -2.37 to -0.69; [Analysis 1.5](#)).

1.6.4 30 mg bifeprunox

We found two trials to be relevant to this subgroup with a total of 622 participants. For this outcome, within this subgroup, we found evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (MD -1.62, 95% CI -2.5 to -0.73; [Analysis 1.5](#)).

1.6.5 40 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 285 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (MD -0.4, 95% CI -1.68 to 0.88; [Analysis 1.5](#)).

1.7 Mental state: 4. Mean change (PANSS GPP subscale, bigger negative value = good)

We found two studies relevant to this outcome and divided the data into four subgroups in accordance with our protocol.

1.7.1 5 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 224 participants. We found evidence of a clear difference between

'bifeprunox' and 'placebo' within this subgroup (MD -2.4, 95% CI -4.76 to -0.04; [Analysis 1.7](#)).

1.7.2 10 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 232 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (MD 0.0, 95% CI -2.29 to 2.29; [Analysis 1.7](#)).

1.7.3 20 mg bifeprunox

We found two trials to be relevant to this subgroup with a total of 549 participants. For this outcome, within this subgroup, we found evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (MD -3.51, 95% CI -4.98 to -2.03; [Analysis 1.7](#)).

1.7.4 30 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 338 participants. For this outcome, within this subgroup, we found evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (MD -3.4, 95% CI -5.34 to -1.46; [Analysis 1.7](#)).

1.8 Mental state: 5. Mean change (BPRS total score, bigger negative value = good)

We identified two studies relevant to this outcome and divided the data into four subgroups in accordance with our protocol.

1.8.1 5 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 224 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (MD -2.4, 95% CI -5.12 to 0.32; [Analysis 1.8](#)).

1.8.2 10 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 232 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (MD 0.4, 95% CI -2.41 to 3.21; [Analysis 1.8](#)).

1.8.3 20 mg bifeprunox

We found two trials to be relevant to this subgroup with a total of 549 participants. For this outcome, within this subgroup, we found evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (MD -4.25, 95% CI -6.02 to -2.48; [Analysis 1.8](#)).

1.8.4 30 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 338 participants. For this outcome, within this subgroup, we found evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (MD -4.0, 95% CI -6.22 to -1.78; [Analysis 1.8](#)).

1.9 Mental state: 6. Mean change (BPRS psychosis cluster, bigger negative value = good)

We found two studies relevant to this outcome and divided the data into four subgroups in accordance with our protocol.

1.9.1 5 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 224 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (MD -0.9, 95% CI -1.93 to 0.13; [Analysis 1.9](#)).

1.9.2 10 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 232 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (MD 0.4, 95% CI -0.72 to 1.52; [Analysis 1.9](#)).

1.9.3 20 mg bifeprunox

We found two trials to be relevant to this subgroup with a total of 549 participants. For this outcome, within this subgroup, we found evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (MD -1.25, 95% CI -1.78 to -0.72; [Analysis 1.9](#)).

1.9.4 30 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 338 participants. For this outcome, within this subgroup, we found evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (MD -1.4, 95% CI -2.23 to -0.57; [Analysis 1.9](#)).

1.10 Mental state: 7. Mean change (CDSS total score, bigger negative value = good)

We found a single study for this outcome and categorised data into two subgroups (in keeping with our protocol).

1.10.1 20 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 324 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (MD -0.4, 95% CI -0.95 to 0.15; [Analysis 1.10](#)).

1.10.2 30 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 338 participants. For this outcome, within this subgroup, we found no evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (MD -0.3, 95% CI -0.85 to 0.25; [Analysis 1.10](#)).

1.11 Leaving study early: 1. Total

We found four studies relevant to this outcome and divided the data into five subgroups in accordance with our protocol.

1.11.1 5 mg bifeprunox

We found one trial to be relevant to this subgroup, with a total of 234 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 0.98, 95% CI 0.78 to 1.21; [Analysis 1.11](#)).

1.11.2 10 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 239 participants. We found no clear difference between 'bifeprunox'

and 'placebo' within this subgroup (RR 1.09, 95% CI 0.89 to 1.33; [Analysis 1.11](#)).

1.11.3 20 mg bifeprunox

We found three trials to be relevant to this subgroup with a total of 863 participants. For this outcome, within this subgroup, we found evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (RR 0.85, 95% CI 0.75 to 0.95; [Analysis 1.11](#)).

1.11.4 30 mg bifeprunox

We found three trials to be relevant to this subgroup with a total of 935 participants. For this outcome, within this subgroup, we found evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (RR 0.89, 95% CI 0.79 to 1.0; [Analysis 1.11](#)).

1.11.5 40 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 297 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 1.01, 95% CI 0.78 to 1.29; [Analysis 1.11](#)).

1.12 Leaving study early: 2. Lack of efficacy

We identified four studies relevant to this outcome and divided the data into five subgroups in accordance with our protocol.

1.12.1 5 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 234 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 0.69, 95% CI 0.4 to 1.18; [Analysis 1.12](#)).

1.12.2 10 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 239 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 1.29, 95% CI 0.83 to 1.98; [Analysis 1.12](#)).

1.12.3 20 mg bifeprunox

We found three trials to be relevant to this subgroup with a total of 863 participants. We found evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 0.66, 95% CI 0.53 to 0.82; [Analysis 1.12](#)).

1.12.4 30 mg bifeprunox

We found three trials to be relevant to this subgroup with a total of 935 participants. For this outcome, within this subgroup, we found evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (RR 0.57, 95% CI 0.45 to 0.72; [Analysis 1.12](#)).

1.12.5 40 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 297 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 0.75, 95% CI 0.44 to 1.27; [Analysis 1.12](#)).

1.13 Leaving study early: 3. Adverse event

We identified four studies relevant to this outcome and categorised data into five subgroups (in keeping with our protocol).

1.13.1 5 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 234 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 0.88, 95% CI 0.41 to 1.87; [Analysis 1.13](#)).

1.13.2 10 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 239 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 0.92, 95% CI 0.44 to 1.92; [Analysis 1.13](#)).

1.13.3 20 mg bifeprunox

We found three trials to be relevant to this subgroup with a total of 863 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 0.95, 95% CI 0.64 to 1.41; [Analysis 1.13](#)).

1.13.4 30 mg bifeprunox

We found three trials to be relevant to this subgroup with a total of 935 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 1.05, 95% CI 0.47 to 2.34). Heterogeneity for this outcome was high ($\chi^2 = 8.02$; $df = 2.0$; $P = 0.02$; $I^2 = 75\%$; [Analysis 1.13](#)).

1.13.5 40 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 297 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 0.74, 95% CI 0.35 to 1.55; [Analysis 1.13](#)).

1.14 Leaving study early: 4. Loss to follow-up

We identified four studies relevant to this outcome and categorised data into five subgroups (in keeping with our protocol).

1.14.1 5 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 234 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 1.72, 95% CI 0.65 to 4.59; [Analysis 1.14](#)).

1.14.2 10 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 239 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 0.66, 95% CI 0.19 to 2.28; [Analysis 1.14](#)).

1.14.3 20 mg bifeprunox

We found three trials to be relevant to this subgroup with a total of 863 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 0.87, 95% CI 0.39 to 1.94; [Analysis 1.14](#)).

1.14.4 30 mg bifeprunox

We found three trials to be relevant to this subgroup with a total of 935 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 1.37, 95% CI 0.61 to 3.1; [Analysis 1.14](#)).

1.14.5 40 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 297 participants. For this outcome, within this subgroup, we found evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (RR 3.69, 95% CI 1.05 to 12.96; [Analysis 1.14](#)).

1.15 Leaving study early: 5. Protocol violation

We identified four studies relevant to this outcome and categorised data into five subgroups (in keeping with our protocol).

1.15.1 5 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 234 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 1.55, 95% CI 0.26 to 9.12; [Analysis 1.15](#)).

1.15.2 10 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 239 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 1.49, 95% CI 0.25 to 8.74; [Analysis 1.15](#)).

1.15.3 20 mg bifeprunox

We found three trials to be relevant to this subgroup with a total of 863 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 1.90, 95% CI 0.69 to 5.24; [Analysis 1.15](#)).

1.15.4 30 mg bifeprunox

We found three trials to be relevant to this subgroup with a total of 935 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 0.99, 95% CI 0.45 to 2.2; [Analysis 1.15](#)).

1.15.5 40 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 297 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 0.72, 95% CI 0.23 to 2.21; [Analysis 1.15](#)).

1.16 Leaving study early: 6. Withdrew consent

We identified four studies relevant to this outcome and categorised data into five subgroups (in keeping with our protocol).

1.16.1 5 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 234 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 1.18, 95% CI 0.7 to 2.0; [Analysis 1.16](#)).

1.16.2 10 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 239 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 0.99, 95% CI 0.57 to 1.72; [Analysis 1.16](#)).

1.16.3 20 mg bifeprunox

We found three trials to be relevant to this subgroup with a total of 863 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 0.93, 95% CI 0.65 to 1.35; [Analysis 1.16](#)).

1.16.4 30 mg bifeprunox

We found three trials to be relevant to this subgroup with a total of 935 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 1.18, 95% CI 0.81 to 1.7; [Analysis 1.16](#)).

1.16.5 40 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 297 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 1.20, 95% CI 0.64 to 2.23; [Analysis 1.16](#)).

1.17 Leaving study early: 7. Other

We found two studies relevant to this outcome and categorised data into four subgroups (in keeping with our protocol).

1.17.1 5 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 234 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 0.34, 95% CI 0.01 to 8.38; [Analysis 1.17](#)).

1.17.2 10 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 239 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 1.98, 95% CI 0.18 to 21.58; [Analysis 1.17](#)).

1.17.3 20 mg bifeprunox

We found two trials to be relevant to this subgroup with a total of 559 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 2.85, 95% CI 0.53 to 15.4; [Analysis 1.17](#)).

1.17.4 30 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 338 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 0.32, 95% CI 0.01 to 7.84; [Analysis 1.17](#)).

1.18 Adverse effects: 1. Total

We found two studies relevant to this outcome and categorised data into four subgroups (in keeping with our protocol) involving 1369 participants. We found no clear difference between 'bifeprunox' and 'placebo' (RR 1.13, 95% CI 0.98 to 1.29).

Heterogeneity for this outcome was high ($\text{Chi}^2 = 25.6$; $\text{df} = 4.0$; $P = 0.0$; $I^2 = 84\%$).

1.18.1 5 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 234 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 1.05, 95% CI 0.95 to 1.15; [Analysis 1.18](#)).

1.18.2 10 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 239 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 1.02, 95% CI 0.92 to 1.13; [Analysis 1.18](#)).

1.18.3 20 mg bifeprunox

We found two trials to be relevant to this subgroup with a total of 558 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 1.10, 95% CI 0.85 to 1.42). This subgroup had important levels of heterogeneity ($\text{Chi}^2 = 6.83$; $\text{df} = 1.0$; $P = 0.01$; $I^2 = 85\%$; [Analysis 1.18](#)).

1.18.4 30 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 338 participants. We found evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 1.44, 95% CI 1.24 to 1.66; [Analysis 1.18](#)).

1.19 Adverse effects: 2. Gastrointestinal: i. Constipation

We found three studies relevant to this outcome and divided the data into five subgroups in accordance with our protocol.

1.19.1 5 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 234 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 1.51, 95% CI 0.73 to 3.1; [Analysis 1.19](#)).

1.19.2 10 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 239 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 0.72, 95% CI 0.3 to 1.73; [Analysis 1.19](#)).

1.19.3 20 mg bifeprunox

We found two trials to be relevant to this subgroup with a total of 536 participants. We found evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 2.71, 95% CI 1.3 to 5.67). Heterogeneity for this subgroup was moderately high ($\text{Chi}^2 = 1.66$; $\text{df} = 1.0$; $P = 0.2$; $I^2 = 39\%$; [Analysis 1.19](#)).

1.19.4 30 mg bifeprunox

We found two trials to be relevant to this subgroup with a total of 593 participants. For this outcome, within this subgroup, we found evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (RR 2.78, 95% CI 1.5 to 5.14; [Analysis 1.19](#)).

1.19.5 40 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 296 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 2.15, 95% CI 0.96 to 4.84; [Analysis 1.19](#)).

1.20 Adverse effects: 2. Gastrointestinal: ii. Dyspepsia

We found two studies relevant to this outcome and categorised data into five subgroups (in keeping with our protocol).

1.20.1 5 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 234 participants. We found evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 2.48, 95% CI 1.24 to 4.96; [Analysis 1.20](#)).

1.20.2 10 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 239 participants. We found evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 2.28, 95% CI 1.14 to 4.58; [Analysis 1.20](#)).

1.20.3 20 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 233 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 1.88, 95% CI 0.91 to 3.9; [Analysis 1.20](#)).

1.20.4 30 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 294 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 2.35, 95% CI 1.0 to 5.54; [Analysis 1.20](#)).

1.20.5 40 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 296 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 2.03, 95% CI 0.84 to 4.88; [Analysis 1.20](#)).

1.21 Adverse effects: 2. Gastrointestinal: iii. GI upset

We found a single study for this outcome and categorised data into three subgroups (in keeping with our protocol).

1.21.1 5 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 234 participants. We found evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 10.35, 95% CI 1.35 to 79.55; [Analysis 1.21](#)).

1.21.2 10 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 239 participants. We found evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 12.89, 95% CI 1.71 to 97.0; [Analysis 1.21](#)).

1.21.3 20 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 233 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 4.18, 95% CI 0.47 to 36.8; [Analysis 1.21](#)).

1.22 Adverse effects: 2. Gastrointestinal: iv. Nausea

We identified four studies relevant to this outcome and categorised data into five subgroups (in keeping with our protocol).

1.22.1 5 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 234 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 1.98, 95% CI 1.0 to 3.91; [Analysis 1.22](#)).

1.22.2 10 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 239 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 1.80, 95% CI 0.9 to 3.6; [Analysis 1.22](#)).

1.22.3 20 mg bifeprunox

We found three trials to be relevant to this subgroup with a total of 861 participants. For this outcome, within this subgroup, we found evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (RR 2.51, 95% CI 1.34 to 4.68). This subgroup had important levels of heterogeneity ($\text{Chi}^2 = 5.18$; $\text{df} = 2.0$; $P = 0.07$; $I^2 = 61\%$; [Analysis 1.22](#)).

1.22.4 30 mg bifeprunox

We found three trials to be relevant to this subgroup with a total of 931 participants. For this outcome, within this subgroup, we found evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (RR 3.41, 95% CI 1.65 to 7.01). Heterogeneity for this outcome was high ($\text{Chi}^2 = 7.06$; $\text{df} = 2.0$; $P = 0.03$; $I^2 = 71\%$; [Analysis 1.22](#)).

1.22.5 40 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 296 participants. We found evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 3.72, 95% CI 1.84 to 7.49; [Analysis 1.22](#)).

1.23 Adverse effects: 2. Gastrointestinal: v. Vomiting

We identified four studies relevant to this outcome and categorised data into five subgroups (in keeping with our protocol).

1.23.1 5 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 234 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 2.07, 95% CI 0.92 to 4.65; [Analysis 1.23](#)).

1.23.2 10 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 239 participants. For this outcome, within this subgroup, we found evidence that 'bifeprunox' was clearly different in its effects when

compared with 'placebo' (RR 2.36, 95% CI 1.07 to 5.17; [Analysis 1.23](#)).

1.23.3 20 mg bifeprunox

We found three trials to be relevant to this subgroup with a total of 861 participants. For this outcome, within this subgroup, we found evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (RR 3.14, 95% CI 1.86 to 5.29; [Analysis 1.23](#)).

1.23.4 30 mg bifeprunox

We found three trials to be relevant to this subgroup with a total of 931 participants. We found evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 2.34, 95% CI 1.26 to 4.35). This subgroup had important levels of heterogeneity ($\text{Chi}^2 = 4.05$; $\text{df} = 2.0$; $P = 0.13$; $I^2 = 50\%$; [Analysis 1.23](#)).

1.23.5 40 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 296 participants. For this outcome, within this subgroup, we found evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (RR 2.03, 95% CI 1.08 to 3.79; [Analysis 1.23](#)).

1.24 Adverse effects: 2. Gastrointestinal: vi. Diarrhoea

We found a single study for this outcome and categorised data into two subgroups (in keeping with our protocol).

1.24.1 30 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 294 participants. For this outcome, within this subgroup, we found evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (RR 9.25, 95% CI 1.19 to 72.08; [Analysis 1.24](#)).

1.24.2 40 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 296 participants. For this outcome, within this subgroup, we found evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (RR 9.12, 95% CI 1.17 to 71.1; [Analysis 1.24](#)).

1.25 Adverse effects: 3. Psychiatric: i. Anxiety

We found two studies relevant to this outcome and categorised data into five subgroups (in keeping with our protocol).

1.25.1 5 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 234 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 1.03, 95% CI 0.34 to 3.12; [Analysis 1.25](#)).

1.25.2 10 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 239 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 1.98, 95% CI 0.77 to 5.11; [Analysis 1.25](#)).

1.25.3 20 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 233 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 1.22, 95% CI 0.42 to 3.51; [Analysis 1.25](#)).

1.25.4 30 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 294 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 1.85, 95% CI 0.64 to 5.39; [Analysis 1.25](#)).

1.25.5 40 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 296 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 1.22, 95% CI 0.38 to 3.9; [Analysis 1.25](#)).

1.26 Adverse effects: 3. Psychiatric: ii. Psychosis aggravated

We found a single study for this outcome and divided the data into three subgroups in accordance with our protocol.

1.26.1 5 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 234 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 0.69, 95% CI 0.2 to 2.38; [Analysis 1.26](#)).

1.26.2 10 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 239 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 1.98, 95% CI 0.77 to 5.11; [Analysis 1.26](#)).

1.26.3 20 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 233 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 0.87, 95% CI 0.27 to 2.77; [Analysis 1.26](#)).

1.27 Adverse effects: 3. Psychiatric: iii. Schizophrenia aggravated

We found a single study for this outcome and divided the data into three subgroups in accordance with our protocol.

1.27.1 5 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 234 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 1.21, 95% CI 0.42 to 3.48; [Analysis 1.27](#)).

1.27.2 10 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 239 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 0.83, 95% CI 0.26 to 2.63; [Analysis 1.27](#)).

1.27.3 20 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 233 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 1.39, 95% CI 0.5 to 3.89; [Analysis 1.27](#)).

1.28 Adverse effects: 4. Extrapyramidal side effects: i. Extrapyramidal disorder

We identified one study relevant to this outcome and divided the data into two subgroups in accordance with our protocol.

1.28.1 30 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 294 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 0.90, 95% CI 0.33 to 2.42; [Analysis 1.28](#)).

1.28.2 40 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 296 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 1.01, 95% CI 0.39 to 2.63; [Analysis 1.28](#)).

1.29 Adverse effects: 4. Extrapyramidal side effects: ii. Tremor

We identified one study relevant to this outcome and categorised data into two subgroups (in keeping with our protocol).

1.29.1 30 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 294 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 1.32, 95% CI 0.51 to 3.45; [Analysis 1.29](#)).

1.29.2 40 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 296 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 1.45, 95% CI 0.57 to 3.7; [Analysis 1.29](#)).

1.30 Adverse effects: 4. Extrapyramidal side effects: iii. Akathisia

We found three studies relevant to this outcome and divided the data into five subgroups in accordance with our protocol.

1.30.1 5 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 234 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 3.10, 95% CI 0.13 to 75.41; [Analysis 1.30](#)).

1.30.2 10 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 239 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 4.96, 95% CI 0.24 to 102.21; [Analysis 1.30](#)).

1.30.3 20 mg bifeprunox

We found two trials to be relevant to this subgroup with a total of 558 participants. For this outcome, within this subgroup, we found evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (RR 6.03, 95% CI 1.59 to 22.82; [Analysis 1.30](#)).

1.30.4 30 mg bifeprunox

We found two trials to be relevant to this subgroup with a total of 632 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 1.83, 95% CI 0.5 to 6.69). Heterogeneity for this subgroup was moderately high ($\chi^2 = 1.78$; $df = 1.0$; $P = 0.18$; $I^2 = 43\%$; [Analysis 1.30](#)).

1.30.5 40 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 296 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 2.03, 95% CI 0.71 to 5.79; [Analysis 1.30](#)).

1.31 Adverse effects: 4. Extrapyramidal side effects: iv. Bradykinesia

We identified one study relevant to this outcome ($n = 296$) and divided the data into two subgroups in accordance with our protocol.

1.31.1 30 mg bifeprunox

No one in either group experienced this adverse effect ([Analysis 1.31](#)).

1.31.2 40 mg bifeprunox

No one in either group experienced this adverse effect ([Analysis 1.31](#)).

1.32 Adverse effects: 4. Extrapyramidal side effects: v. Choreoathetosis

We identified one study relevant to this outcome and categorised data into two subgroups (in keeping with our protocol).

1.32.1 30 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 294 participants. No one in either group experienced this adverse effect ([Analysis 1.32](#)).

1.32.2 40 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 296 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 3.04, 95% CI 0.12 to 74.04; [Analysis 1.32](#)).

1.33 Adverse effects: 4. Extrapyramidal side effects: vi. Cogwheel rigidity

We identified one study relevant to this outcome and divided the data into two subgroups in accordance with our protocol.

1.33.1 30 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 294 participants. We found no evidence of a clear difference between

'bifeprunox' and 'placebo' for this subgroup (RR 3.08, 95% CI 0.13 to 75.05; [Analysis 1.33](#)).

1.33.2 40 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 296 participants. No one in either group experienced this adverse effect ([Analysis 1.33](#)).

1.34 Adverse effects: 4. Extrapyramidal side effects: vii. Dyskinesia

We identified two studies relevant to this outcome and categorised data into three subgroups (in keeping with our protocol).

1.34.1 20 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 325 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 2.09, 95% CI 0.19 to 22.8; [Analysis 1.34](#)).

1.34.2 30 mg bifeprunox

We found two trials to be relevant to this subgroup with a total of 632 participants. For this outcome, within this subgroup, we found evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (RR 8.47, 95% CI 1.56 to 45.87; [Analysis 1.34](#)).

1.34.3 40 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 296 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 9.12, 95% CI 0.5 to 167.93; [Analysis 1.34](#)).

1.35 Adverse effects: 4. Extrapyramidal side effects: viii. Dystonia

We found a single study for this outcome and divided the data into two subgroups in accordance with our protocol.

1.35.1 30 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 294 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 3.08, 95% CI 0.32 to 29.3; [Analysis 1.35](#)).

1.35.2 40 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 296 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 3.04, 95% CI 0.32 to 28.9; [Analysis 1.35](#)).

1.36 Adverse effects: 4. Extrapyramidal side effects: ix. Parkinsonism

We identified one study ($n = 296$) relevant to this outcome and categorised data into two subgroups (in keeping with our protocol).

1.36.1 30 mg bifeprunox

No one in either group experienced this adverse effect ([Analysis 1.36](#)).

1.36.2 40 mg bifeprunox

No one in either group experienced this adverse effect ([Analysis 1.36](#)).

1.37 Adverse effects: 4. Extrapyramidal side effects: x. Tardive dyskinesia

We identified one study relevant to this outcome and divided the data into two subgroups in accordance with our protocol.

1.37.1 30 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 294 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 5.14, 95% CI 0.25 to 106.09; [Analysis 1.37](#)).

1.37.2 40 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 296 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 3.04, 95% CI 0.12 to 74.04; [Analysis 1.37](#)).

1.38 Adverse effects: 5. Lipid profile: i. Mean change (Total cholesterol, bigger negative value = good)

We found two studies relevant to this outcome and divided the data into three subgroups in accordance with our protocol.

1.38.1 20 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 259 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (MD -3.6, 95% CI -11.18 to 3.98; [Analysis 1.38](#)).

1.38.2 30 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 255 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (MD -3.8, 95% CI -12.14 to 4.54; [Analysis 1.38](#)).

1.38.3 Bifeprunox total

We found one trial to be relevant to this subgroup with a total of 260 participants. For this outcome, within this subgroup, we found evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (MD -8.9, 95% CI -16.29 to -1.51; [Analysis 1.38](#)).

1.39 Adverse effects: 5. Lipid profile: ii. Mean change (Triglycerides, bigger negative value = good)

We identified two studies relevant to this outcome and divided the data into three subgroups in accordance with our protocol.

1.39.1 20 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 259 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (MD 3.0, 95% CI -20.18 to 26.18; [Analysis 1.39](#)).

1.39.2 30 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 255 participants. We found evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (MD -23.6, 95% CI -47.02 to -0.18; [Analysis 1.39](#)).

1.39.3 Bifeprunox total

We found one trial to be relevant to this subgroup with a total of 260 participants. For this outcome, within this subgroup, we found evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (MD -23.8, 95% CI -41.15 to -6.45; [Analysis 1.39](#)).

1.40 Adverse effects: 5. Lipid profile: iii. Mean change (VLDL, bigger negative value = good)

We identified one study relevant to this outcome and divided the data into two subgroups in accordance with our protocol.

1.40.1 20 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 259 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (MD 0.6, 95% CI -3.28 to 4.48; [Analysis 1.40](#)).

1.40.2 30 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 255 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (MD -2.8, 95% CI -6.58 to 0.98; [Analysis 1.40](#)).

1.41 Adverse effects: 5. Lipid profile: iv. Mean change (LDL, bigger negative value = good)

We found two studies relevant to this outcome and divided the data into three subgroups in accordance with our protocol.

1.41.1 20 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 259 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (MD 0.6, 95% CI -6.6 to 7.8; [Analysis 1.41](#)).

1.41.2 30 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 255 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (MD 1.2, 95% CI -6.18 to 8.58; [Analysis 1.41](#)).

1.41.3 Bifeprunox total

We found one trial to be relevant to this subgroup with a total of 252 participants. For this outcome, within this subgroup, we found evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (MD -6.6, 95% CI -13.07 to -0.13; [Analysis 1.41](#)).

1.42 Adverse effects: 5. Lipid profile: v. Mean change (HDL, bigger negative value = bad)

We found two studies relevant to this outcome and categorised data into three subgroups (in keeping with our protocol).

1.42.1 20 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 259 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (MD -1.7, 95% CI -4.88 to 1.48; [Analysis 1.42](#)).

1.42.2 30 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 255 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (MD 0.2, 95% CI -3.18 to 3.58; [Analysis 1.42](#)).

1.42.3 Bifeprunox total

We found one trial to be relevant to this subgroup with a total of 260 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (MD 1.7, 95% CI -1.24 to 4.64; [Analysis 1.42](#)).

1.43 Adverse effects: 5. Lipid profile: vi. TG:HDL ratio (bigger negative value = good)

We identified one study relevant to this outcome with a total of 260 participants. There were no subgroups in this outcome. We found evidence of a clear difference between 'bifeprunox' and 'placebo' for this outcome (MD -0.7, 95% CI -1.21 to -0.19; [Analysis 1.43](#)).

1.44 Adverse effects: 6. Weight: i. Mean change (kg, bigger positive value = bad)

We found a single study for this outcome with a total of 483 participants. There were no subgroups in this outcome. We found no evidence of a clear difference between the two treatments (MD -0.6, 95% CI -1.22 to 0.02; [Analysis 1.44](#)).

1.45 Adverse effects: 6. Weight: ii. Total number of participants with $\geq 7\%$ weight increase

We identified one study relevant to this outcome with a total of 483 participants. There were no subgroups in this outcome. We found no evidence of a clear difference between the two treatments (RR 1.02, 95% CI 0.31 to 3.33; [Analysis 1.45](#)).

1.46 Adverse effects: 6. Weight: iii. Total number of participants with $\geq 7\%$ weight decrease

We identified one study relevant to this outcome with a total of 483 participants. There were no subgroups in this outcome. We found no evidence of a clear difference between the two treatments (RR 1.3, 95% CI 0.66 to 2.54; [Analysis 1.46](#)).

1.47 Adverse effects: 6. Weight iv. Appetite decrease

We identified two studies relevant to this outcome and categorised data into five subgroups (in keeping with our protocol).

1.47.1 5 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 234 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 3.62, 95% CI 0.77 to 17.07; [Analysis 1.47](#)).

1.47.2 10 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 239 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 0.50, 95% CI 0.05 to 5.4; [Analysis 1.47](#)).

1.47.3 20 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 233 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 3.13, 95% CI 0.65 to 15.2; [Analysis 1.47](#)).

1.47.4 30 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 294 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 3.43, 95% CI 0.96 to 12.19; [Analysis 1.47](#)).

1.47.5 40 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 296 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 2.70, 95% CI 0.73 to 9.99; [Analysis 1.47](#)).

1.48 Adverse effects: 6. Weight: v. Anorexia

We found two studies relevant to this outcome and divided the data into three subgroups in accordance with our protocol.

1.48.1 20 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 325 participants. We found evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 19.83, 95% CI 1.16 to 337.92; [Analysis 1.48](#)).

1.48.2 30 mg bifeprunox

We found two trials to be relevant to this subgroup with a total of 632 participants. We found evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 10.03, 95% CI 1.08 to 92.99). This subgroup had moderate levels of heterogeneity ($\text{Chi}^2 = 1.61$; $\text{df} = 1.0$; $P = 0.2$; $I^2 = 37\%$; [Analysis 1.48](#)).

1.48.3 40 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 296 participants. We found evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 9.12, 95% CI 1.17 to 71.1; [Analysis 1.48](#)).

1.49 Adverse effects: 7. Pain: i. General pain

We identified two studies relevant to this outcome and divided the data into four subgroups in accordance with our protocol.

1.49.1 5 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 234 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 3.1, 95% CI 0.86 to 11.18; [Analysis 1.49](#)).

1.49.2 10 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 239 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 1.65, 95% CI 0.4 to 6.76; [Analysis 1.49](#)).

1.49.3 20 mg bifeprunox

We found two trials to be relevant to this subgroup with a total of 536 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 1.97, 95% CI 0.74 to 5.23; [Analysis 1.49](#)).

1.49.4 30 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 299 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 1.66, 95% CI 0.4 to 6.8; [Analysis 1.49](#)).

1.50 Adverse effects: 7. Pain: ii. Back pain

We found a single study for this outcome and categorised data into two subgroups (in keeping with our protocol).

1.50.1 20 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 303 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 3.87, 95% CI 0.84 to 17.93; [Analysis 1.50](#)).

1.50.2 30 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 299 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 0.50, 95% CI 0.05 to 5.42; [Analysis 1.50](#)).

1.51 Adverse effects: 7. Pain: iii. Arthralgia

We identified one study relevant to this outcome and divided the data into two subgroups in accordance with our protocol.

1.51.1 20 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 303 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 6.77, 95% CI 0.84 to 54.38; [Analysis 1.51](#)).

1.51.2 30 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 299 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 2.98, 95% CI 0.31 to 28.32; [Analysis 1.51](#)).

1.52 Adverse effect: 8. Other: i. Asthenia

We found a single study for this outcome and divided the data into two subgroups in accordance with our protocol.

1.52.1 20 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 325 participants. We found no clear difference between 'bifeprunox'

and 'placebo' within this subgroup (RR 11.48, 95% CI 0.64 to 205.95; [Analysis 1.52](#)).

1.52.2 30 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 338 participants. For this outcome, within this subgroup, we found evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (RR 18.34, 95% CI 1.08 to 312.62; [Analysis 1.52](#)).

1.53 Adverse effects: 8. Other: ii. Dysmenorrhoea

We identified one study relevant to this outcome and divided the data into three subgroups in accordance with our protocol.

1.53.1 5 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 234 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 3.10, 95% CI 0.13 to 75.41; [Analysis 1.53](#)).

1.53.2 10 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 239 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 4.96, 95% CI 0.24 to 102.21; [Analysis 1.53](#)).

1.53.3 20 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 233 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 3.13, 95% CI 0.13 to 76.06; [Analysis 1.53](#)).

1.54 Adverse effects: 8. Other: iii. Dry mouth

We found two studies relevant to this outcome and categorised data into three subgroups (in keeping with our protocol).

1.54.1 20 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 303 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 2.58, 95% CI 0.7 to 9.54; [Analysis 1.54](#)).

1.54.2 30 mg bifeprunox

We found two trials to be relevant to this subgroup with a total of 593 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 2.17, 95% CI 0.66 to 7.09; [Analysis 1.54](#)).

1.54.3 40 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 296 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 1.01, 95% CI 0.06 to 16.05; [Analysis 1.54](#)).

1.55 Adverse effects: 8. Other: iv. Fatigue

We found a single study for this outcome and divided the data into two subgroups in accordance with our protocol.

1.55.1 30 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 294 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 0.34, 95% CI 0.04 to 3.26; [Analysis 1.55](#)).

1.55.2 40 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 296 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 1.01, 95% CI 0.21 to 4.94; [Analysis 1.55](#)).

1.56 Adverse effects: 8. Other: v. Vaginitis

We found a single study for this outcome and divided the data into two subgroups in accordance with our protocol.

1.56.1 30 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 294 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 5.14, 95% CI 0.25 to 106.09; [Analysis 1.56](#)).

1.56.2 40 mg bifeprunox

No one in either group experienced this adverse effect ([Analysis 1.56](#)).

1.57 Adverse effects: 8. Other: vi. Dizziness

We found two studies relevant to this outcome and divided the data into three subgroups in accordance with our protocol.

1.57.1 20 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 325 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 1.74, 95% CI 0.42 to 7.16; [Analysis 1.57](#)).

1.57.2 30 mg bifeprunox

We found two trials to be relevant to this subgroup with a total of 632 participants. For this outcome, within this subgroup, we found evidence that 'bifeprunox' was clearly different in its effects when compared with 'placebo' (RR 3.02, 95% CI 1.05 to 8.62). This subgroup had moderate levels of heterogeneity ($\chi^2 = 1.87$; $df = 1.0$; $P = 0.17$; $I^2 = 46\%$; [Analysis 1.57](#)).

1.57.3 40 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 296 participants. We found evidence of a clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 3.38, 95% CI 1.4 to 8.17; [Analysis 1.57](#)).

1.58 Adverse effects: 8. Other: vii. Somnolence

We identified one study relevant to this outcome and categorised data into two subgroups (in keeping with our protocol).

1.58.1 20 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 303 participants. We found no clear difference between 'bifeprunox'

and 'placebo' within this subgroup (RR 0.69, 95% CI 0.22 to 2.13; [Analysis 1.58](#)).

1.58.2 30 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 299 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 0.57, 95% CI 0.17 to 1.9; [Analysis 1.58](#)).

1.59 Adverse effects: 8. Other: viii. Sedation

We found two studies relevant to this outcome and categorised data into three subgroups (in keeping with our protocol).

1.59.1 20 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 303 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 1.29, 95% CI 0.46 to 3.63; [Analysis 1.59](#)).

1.59.2 30 mg bifeprunox

We found two trials to be relevant to this subgroup with a total of 593 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 2.07, 95% CI 0.9 to 4.76; [Analysis 1.59](#)).

1.59.3 40 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 296 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 2.03, 95% CI 0.38 to 10.9; [Analysis 1.59](#)).

1.60 Adverse effects: 8. Other: ix. Nasopharyngitis

We identified one study relevant to this outcome and categorised data into two subgroups (in keeping with our protocol).

1.60.1 20 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 303 participants. We found no clear difference between 'bifeprunox' and 'placebo' within this subgroup (RR 2.26, 95% CI 0.59 to 8.57; [Analysis 1.60](#)).

1.60.2 30 mg bifeprunox

We found one trial to be relevant to this subgroup with a total of 299 participants. We found no evidence of a clear difference between 'bifeprunox' and 'placebo' for this subgroup (RR 1.32, 95% CI 0.3 to 5.82; [Analysis 1.60](#)).

DISCUSSION

Summary of main results

1. BIFEPRUNOX versus PLACEBO for schizophrenia

Bifeprunox is not available and will probably never be available. The state of the evidence in this review is very poor. We are aware that there are more unpublished, unavailable data and have requested more information from authors and companies. These requests have largely been met with silence, with no more data forthcoming. We identified other trials that were discontinued "due to lack of efficacy". The data we have summarised below is limited,

and probably biased, suggesting that bifeprunox is an interesting compound, but not convincing those interested in the treatment of schizophrenia are missing out on an important drug.

1. Mental state: Mean change - PANSS positive and negative subscales

We identified two trials reporting on these mental state outcomes ($n = 549$). Bifeprunox was statistically significantly more effective than placebo at improving both the positive symptoms and negative symptoms of schizophrenia, but the clinical meaning of these data is far from clear. It is likely that one or two points difference in these scales is of little import. In addition, these data were rated as of 'low' quality.

2. Service use: Re-admission

No studies reported on this important outcome. Unfortunately, it is not rare for trials to ignore important service-level outcomes in favour of rating-scale measures (which are almost never used in clinical practice) (Miyar 2012).

3. Global state: Deteriorated

One study reported on this outcome and showed that bifeprunox 20 mg was more effective than placebo at preventing deterioration compared with placebo. However, as these data were of very low quality, it is difficult to draw definitive conclusions regarding the drug's efficacy.

4. Quality of life: Important change

No studies reported on this outcome.

5. Adverse effects

5.1 Weight

We found no difference in weight change in people allocated to bifeprunox when compared with placebo. This finding could have been important as weight gain is a common problem with other antipsychotic drugs. Bifeprunox also showed an advantageous lipid profile, with lower levels of cholesterol, triglycerides, very low-density lipoprotein, low-density lipoprotein, and triglycerides:high-density lipoprotein ratio. Bifeprunox also did not significantly reduce high-density lipoprotein levels, which have been shown to have a protective effect against coronary heart disease (Li 2004). We judged these data to be of 'moderate' quality.

However, much lipid and weight data could not be used for analysis because of missing standard deviations and unclear graphical reporting. From visual inspection of these problematic data, bifeprunox outcomes appear better than those associated with use of placebo. Bifeprunox use led to a significantly increased risk of loss of appetite or anorexia. These are important findings should bifeprunox someday be used clinically.

5.2 Others

The data from the trials suggest that bifeprunox has a positive extrapyramidal symptom (EPS) profile. This could have been important as many antipsychotic drugs have been associated with EPS (Peluso 2012). Only akathisia, a movement disorder of inner restlessness and need to be in constant motion, was significantly more prevalent in the bifeprunox group compared with placebo, so whilst bifeprunox may have an overall favourable EPS profile when

compared to other antipsychotics, it is still associated with some movement problems.

It should be noted that some other adverse events were significantly higher in the bifeprunox groups such as arthralgia, nausea, vomiting, diarrhoea, and dyspepsia. One study reported three deaths across both bifeprunox and control groups (Casey 2007). The study stated that the deaths were not attributed to the drug.

6. Economics: Cost

No studies reported on this potentially important outcome.

7. Leaving study early

Bifeprunox resulted in more people staying in the study, which if the result of a genuine decrease in symptoms of schizophrenia, could be seen as encouraging. Certainly, fewer participants taking bifeprunox left studies 'due to lack of efficacy'. Also, there were no significant differences between bifeprunox and placebo participants leaving the study early due to adverse events.

Overall completeness and applicability of evidence

1. Completeness

The findings from this review are significantly weakened by the limited amount of available data. The search strategy identified four relevant trials (total $n = 2289$ people). We found one report suggesting that efficacy and safety data had been gathered from around 2500 participants; we have therefore failed to identify data from more than 200 people. We were unable to extract much data for key outcomes and worried about data lost, poorly reported, and data for which informed consent was gained but never honoured. Our requests of lead authors for more information were met with no response. Another two trials were started but then terminated with no data being published. One company supporting these trials did not respond when contacted in October 2015, whilst another company responded in November 2015 saying the company had sold off its pharmaceutical division.

2. Applicability

Most of the studies included people with acute exacerbation of schizophrenia, although two studies included people with stable schizophrenia. The two different inclusion criteria allows for a certain degree of generalisation. However, it should be noted that these trials were not conducted in real-world scenarios or across a diverse range of countries (and thus healthcare systems). Generalisability of the results to the worldwide population of people with schizophrenia would therefore have been difficult should the drug have been widely circulated for use. The doses of bifeprunox used varied from 5 mg to 40 mg, although the results of this review are largely based on the 20 mg dose.

3. Homogeneity

Some results are yet even more difficult to interpret because of heterogeneity. The test for homogeneity is based on I^2 analysis, and is often fairly weak, as, for this review, when the number of studies is small.

Quality of the evidence

We found the quality of the current evidence to be low based on GRADE ratings (Schünemann 2008). No study reported on the method of randomisation in detail or described the method of allocation concealment. All studies were reported to be double blind, but it was not clear whether assessors were blinded to the treatment groups. No details were given regarding the placebo, so it was impossible to tell whether participants could work out which group they had been allocated to, which would have compromised blinding. In terms of funding, we rated all trials as at high risk of bias, as they were sponsored by the interested drug company. However, as these companies were the only ones with access to bifeprunox, this was unavoidable. Some evidence was presented with results of various doses of bifeprunox pooled together, which made identifying an optimum dose impossible. Several studies presented data only in graphs, making it difficult to extract accurate data. Furthermore, several outcomes were presented as just statistical measures of probability (P values), which made it impossible to acquire raw data for synthesis. P values were also used to show association between intervention and outcomes instead of showing the actual strength of the association. Although P values are influenced by the strength of association, they also depend on the sample size of the groups involved. As a result, much potentially informative data could not be used.

Potential biases in the review process

1. Failing to identify trials

While this review involved meticulous searching, it is possible that trials remained undetected. We have reason to suspect this, as we

have identified documentation suggesting that at least 2500 people were involved in trials, when the total number from all of the studies included in this review falls more than 200 short of this.

2. Failing to identify data for extraction

Whilst this review involved careful and precise data extraction, it is possible that some values were missed or misread due to poor quality of conference posters.

Agreements and disagreements with other studies or reviews

We know of no other reviews on bifeprunox. However, it could be argued that the decision of the US Food and Drug Administration (FDA) to reject the drug was a review in itself. It seems likely that the FDA had more data to work with than us, but we have been unable to find any on the FDA website. The FDA, which acknowledged some efficacy of bifeprunox, did not approve the drug for acute or long-term symptoms of schizophrenia because more research was required to demonstrate convincing effects beyond those already achieved with currently licensed drugs (Jeffrey 2007; Ye 2014). The FDA also had concerns over one death that appeared to be the result of a hepatotoxic reaction to bifeprunox.

The drug development was halted shortly after the FDA judgement to reject its use (Table 2). We are not in a position to affirm or dispute the FDA's opinion. Based on the very limited information we have, the data for bifeprunox do not seem that different to those of other licensed compounds. It would seem important to release all relevant data, especially because some of these data relate to currently used compounds and could add to the information on them.

Figure 3. Safety alert letter from Solvay mentioning participant death from 2004.

Figure 4. Pathologist's report on cause of death of 2004 participant.

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AFIP Consultation Report

<u>AFIP ACCESSION NO.</u>	<u>SEQUENCE NO.</u>
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K, A B.	SSN:
A-07-186 B S	ZDG
November 29, 2007	

Earls Sands, MD
Solvay Pharmaceuticals, Inc.
901 Sawyer Road
Marietta, GA 30062

DIAGNOSIS: Liver: Microvesicular steatosis, suggestive of toxic injury
Kidney: Nonspecific changes
Brain: Mild Alzheimer type II gliosis and microglial activation

The liver shows microvesicular steatosis with hepatocellular cytoplasmic fat droplets that range from barely visible at high magnification to several times the size of the nucleus. A Masson trichrome stain shows no significant fibrosis, while an iron stain shows only minimal hemosiderin granules. Despite the history of abnormal liver tests three months previously, there is no evidence of underlying chronic liver disease. There is also nothing to suggest acetaminophen (paracetamol) toxicity or injury secondary to hypotension, both of which typically cause zone 3 ("centrilobular") coagulative necrosis. In view of the history, it seems most likely that the microvesicular steatosis associated with aminotransferase elevations and severe metabolic abnormalities (metabolic acidosis, hypoglycemia) as well as renal dysfunction and coma represent a toxic reaction to the investigational drug, probably due to mitochondrial toxicity.

The sections of kidney and brain were reviewed by the Divisions of Nephropathology and Neuropathology respectively. The kidney was noted to show only nonspecific changes with a mild increase in glomerular mesangial matrix and patchy interstitial edema. The brain was noted to have mild Alzheimer type II gliosis and microglial activation, also considered nonspecific.

A copy of this report has been faxed to you at 770-578-5864. We are returning the paraffin blocks, as you requested, under separate cover.

 Zachary D. Goodman, M.D., Ph.D.
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Page 1 of 2

Figure 5. Safety alert from Solvay announcing suspension of all bifeprunox studies.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with schizophrenia

There are concerns that the FDA's decision to cease development of bifeprunox could be causing people with schizophrenia to miss out on a potentially effective treatment. This review reports a promising efficacy profile and, importantly, a favourable adverse effect profile in terms of weight gain and extrapyramidal symptoms. However, these findings have been drawn from few trials, the data from which we have rated as low quality, with some missing data. In 2004, one person given bifeprunox died, and when we requested further details of this from the drug company, we found no evidence that they felt it was possible to argue that use of the drug was still of value for people with schizophrenia.

People with schizophrenia entered these trials - we presume - with the expectation that their data would be made available and not hidden. Even if bifeprunox is never to be used, data in these trials remain that could inform efficacy regarding other compounds. Assuming compliance with the letter of the law, we suggest that the altruistic spirit in which people agreed to be randomised still has not been honoured by Solvay, Lundbeck, and Wyeth Pharmaceuticals.

2. For clinicians

Bifeprunox may never come to market. It may be effective at treating symptoms of schizophrenia, with a somewhat favourable adverse effect profile - although the one death, details about which remain opaque, remains a worry. The data presented in this review would be more important if bifeprunox were to be re-introduced to the market. The main issue for clinicians is not about bifeprunox but rather the missing data from these trials that is relevant to other compounds currently in use.

3. For policymakers/funders

This review, of a drug that may well remain dead to the market, is an excellent illustration of the need for all data to be openly accessible. It seems a company has moved on from this research and left, buried in its vaults, behind the silencing contractual agreements with researchers, data that could be of use to people with schizophrenia taking drugs that are in everyday use. Policymakers should encourage the liberation of all data. The FDA's website suggests that data will be open and decisions will be traceable. This may be the case, but the actual difficulty in finding these documents or data sets effectively makes all this important information out of reach of the ordinary researcher. This, surely, cannot be the aim of those to whom the FDA is responsible.

Implications for research

1. General

Following Consolidated Standards of Reporting Trials (CONSORT) for good reporting of randomisation, identification of participants, and description of interventions would have helped to increase

the data available for this review and also improve the quality of evidence (Moher 2010). Clear, unique study numbers would have helped researchers identify whether we had found multiple studies or just multiple/salami publications. The best example of this from our review is the Shapira 2007b report of the Bourin 2007 study. In this single report, data were presented that seemed to be from another, unidentified six-week study. These data have been wasted.

It should be a minimum requirement that all data be presented in numbers to allow for statistical analysis. Continuous data should be presented with means, standard deviations (or standard errors), and the number of participants should be clearly stated; this was not always the case in the studies in this review. Much data from these trials was presented in graphs or P values, which were of limited value and as a result, despite there being over 2000 people in the included trials, large amounts of data could not be used due to poor reporting. Intention-to-treat analysis should be performed on all outcomes, and all trial data should be easily accessible. We were presented with just conference posters on some occasions and contacting the lead authors proved fruitless and so, once again, data were lost.

2. Specific

2.1 Reviews

This review featured studies containing treatment arms not relevant to this review. Data from these treatment arms could be used in other reviews (Table 1) to, at the very least, improve their precision. If bifeprunox were to be revived in the future, then data extracted in this review could be used to compare it to other available treatments as well as to find the optimum dose of bifeprunox.

2.2 Trials

We do not believe that more trials of bifeprunox should be conducted. We say this more out of respect of the FDA's decision than from evidence found and used in this review. However, should attempts to revive the use of bifeprunox be made, we have given some thought about how an 'ideal' trial should be conducted and present this in Table 3. Before such an investment be made, all data from the current studies should be made available so they can be analysed properly. Whilst the drug companies made efforts to understand the circumstances of the death that occurred in 2004, the fact that the trials were ceased (and never restarted) within two months suggests real safety concerns surrounding the drug that would need to be addressed before trials could recommence.

ACKNOWLEDGEMENTS

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.

We would like to thank Alexandra Harkness (AH), Alice McDermott (AM), and Anna Yates (AY) for their contributions to previous versions of this review.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Barbato 2006

Methods	Allocation: randomised. Blinding: double. Duration: 6 weeks. Design: parallel. Country: not reported. Setting: hospital.
Participants	Diagnosis: schizophrenia (DSM-IV-TR). N = 604. Sex: 437 M, 167 F. Age: 18-73 years, average ~ 39.2 years. History: acute exacerbation. Included: baseline PANSS between 70 and 120 (inclusive), score of 4 or above on at least 2 of the following PANSS items: conceptual disorganisation, hallucinatory behavior, suspiciousness, or unusual thought content, and, score of 4 or above on the CGI-S. Excluded: not reported.

Bifeprunox versus placebo for schizophrenia (Review)

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Barbato 2006 (Continued)

Interventions	1. Bifeprunox: dose 20mg/day. N = 154. 2. Bifeprunox: dose 30mg/day. N = 150. 3. Placebo. N = 150. 4. Olanzapine. N = 150. Medication given fixed-dose regimen; titration to full dose from 0.25mg for bifeprunox over 7-8 days; titration to full dose from 10mg for olanzapine over 7 days.
Outcomes	Leaving study early. Adverse effects. Unable to use - Mental state: PANSS (no SD). Weight measures (no useable data).
Notes	Review uses bifeprunox and placebo data only. No response when contacting lead author.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Patients randomly assigned' - no further description.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for leaving the study early fully reported, according to group.
Selective reporting (reporting bias)	High risk	Not all expected outcomes reported.
Other bias	High risk	"Study supported by H. Lundbeck A/S, Solvay Pharmaceuticals, Inc., and Wyeth Pharmaceuticals".

Bourin 2007

Methods	Allocation: randomised.
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Bifeprunox versus placebo for schizophrenia (Review)

Bourin 2007 (Continued)

	<p>Blinding: double.</p> <p>Duration: 6 months.</p> <p>Design: parallel.</p> <p>Country: not reported.</p> <p>Setting: not reported.</p>
Participants	<p>Diagnosis: schizophrenia (DSM-IV-TR).</p> <p>N = 497 (subgroup analysis on group of 350).</p> <p>Sex: 269 M, 228 F.</p> <p>Age: 18-65 years, average ~ 40.1 years.</p> <p>History: stable schizophrenia** + acutely exacerbated schizophrenia.</p> <p>Included: schizophrenia 2+ years, no modification of treatment for 30 days. PANSS score > 60, item P7 and G8 < 4, CGI-S > 4.</p> <p>**For subgroup analysis, a more stringent definition of stability was used where current antipsychotic usage remained unchanged for 3 months (rather than 1) prestudy and under 3 additional conditions: dose reductions, dosing holidays less than or equal to 7 days and washout for less than ten days before first bifeprunox dose was permitted.</p> <p>Excluded: not reported.</p>
Interventions	<p>1. Bifeprunox: dose 20mg/day. N = 159 (109 in subgroup analysis).</p> <p>2. Bifeprunox: dose 30mg/day. N = 172 (119 in subgroup analysis).</p> <p>3. Placebo. N = 166 (122 in subgroup analysis).</p> <p>Titration from 0.25mg, over 7-8 days, until full dose reached.</p>
Outcomes	<p>Global state: CGI-S, CGI-I and 'Deteriorated'*** (CGI-I of 5 or greater or PANSS P7 and/or G8 of 5 or greater for 2 days or at least 20% increase in PANSS total score).</p> <p>Mental state: BPRS, CDSS, PANSS</p> <p>Leaving study early.</p> <p>Adverse effects.</p> <p>Unable to use -</p> <p>Time to deterioration (only P values presented).</p>
Notes	<p>Time to deterioration calculated from PANSS and CGI measures.</p> <p>**Subgroup analysis was done on a group of 350, the outcome of deterioration was for this subgroup only so there is no overall group data for this.</p> <p>No response when contacting lead author.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized" no further information reported.

Bifeprunox versus placebo for schizophrenia (Review)

Bourin 2007 (Continued)

Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind" no further information reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All-patients-treated-set, used to assess safety measures. Full-analysis-set, used to assess efficacy measures.
Selective reporting (reporting bias)	Low risk	All outcomes reported, except 1 subgroup BMI measure.
Other bias	High risk	"Study supported by H. Lundbeck A/S, Solvay Pharmaceuticals, Inc., and Wyeth Pharmaceuticals."

Casey 2007

Methods	Allocation: randomised. Blinding: double. Duration: 6 weeks. Design: parallel. Country: USA and Canada. Setting: hospital.
Participants	Diagnosis: schizophrenia (DSM-IV-TR). N = 589. Sex: 429 M, 140 F. Age: mean = 40.8 years. History: acute exacerbation. Included: baseline PANSS between 70 and 120 (inclusive), score of 4 or above on at least 2 of the following PANSS items: conceptual disorganisation, hallucinatory behavior, suspiciousness, or unusual thought content, and, score of 4 or above on the CGI - S. Excluded: co-occurring psychiatric diagnosis thought to interfere, substance or alcohol abuse (except cannabinoid, nicotine, caffeine), suicide or violent behaviour, treatment resistant, hospitalised for current psychotic episode > 4 weeks, showing clinically abnormal vital signs/laboratory values, other cardiovascular illness.
Interventions	1. Bifeprunox: dose 5mg/day. N = 115. 2. Bifeprunox: dose 10mg/day. N = 120. 3. Bifeprunox: dose 20mg/day. N = 115.

Bifeprunox versus placebo for schizophrenia (Review)

Casey 2007 (Continued)

4. Placebo. N = 119.
5. Risperidone: dose 6mg/day. N = 120.
- Titrated up according to forced-dose titration schedule, until target dose is reached.

Outcomes	Global state: CGI-S, CGI-I. Mental state: BPRS, PANSS. Leaving study early. Adverse effects. Unable to use - Global state: time to deterioration (P values only, no mean, no SD). Weight measures (no usable data). Lipid profile measures (no usable data).
Notes	20 participants not accounted for after randomisation stage. Review uses bifeprunox and placebo data only. No response when contacting lead author.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"patients were randomized to one of five treatment arms" no further information given.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Efficacy analyses were performed on the intent-to-treat (ITT) population, using both last observations carried forward (LOCF) and observed case (OC) data sets" Reasons for leaving study clearly reported.
Selective reporting (reporting bias)	Unclear risk	All expected outcomes reported, some means and SDs omitted.
Other bias	High risk	"Study supported by H. Lundbeck A/S, Solvay Pharmaceuticals, Inc., and Wyeth Pharmaceuticals."

Meltzer 2007

Methods	Allocation: randomised. Blinding: double. Duration: 6 weeks. Design: parallel. Country: USA. Setting: not reported.
Participants	Diagnosis: schizophrenia (DSM-IV-TR). N = 599. Sex: 396 M, 203 F. Age: 18-69 years, average ~ 37.8 years. History: acute exacerbation. Included: baseline PANSS between 70 and 120 (inclusive), score of 4 or above on at least 2 of the following PANSS items: conceptual disorganisation, hallucinatory behavior, suspiciousness, or unusual thought content, and, score of 4 or above on the CGI - S. Excluded: not reported.
Interventions	1. Bifeprunox: dose 30mg/day. N = 148. 2. Bifeprunox: dose 40mg/day. N = 148. 3. Placebo. N = 149. 4. Risperidone: dose 6mg/day. N = 154. 3 day wash-out period. Bifeprunox titrated from 0.25mg, doubled daily, until dose reached at day 8.
Outcomes	Global state: CGI-S. Mental state: PANSS positive sub-scale, PANSS negative sub-scale. Leaving study early. Adverse effects. Unable to use - Global state: responder rate (no usable data). Mental state: PANSS total score (no usable data). Mental state: PANSS general psychopathology sub-scale (no usable data). Mental state: PANSS responder rate (no usable data). Mental state: BPRS (no usable data). Weight measures (no usable data). Lipid profile measures (no usable data). Prolactin measures (no usable data).
Notes	Review uses bifeprunox and placebo data only.

Bifeprunox versus placebo for schizophrenia (Review)

Meltzer 2007 (Continued)

No response when contacting lead author.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized" no further information reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind" no further information reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"analysis was based on Intention-to-Treat population using last observation carried forward" and thorough reporting of reasons for leaving study early across groups.
Selective reporting (reporting bias)	Unclear risk	All outcomes reported however some means and SDs omitted.
Other bias	High risk	"Study supported by H. Lundbeck A/S, Solvay Pharmaceuticals, Inc., and Wyeth Pharmaceuticals."

BMI: body mass index

BPRS: Brief Psychiatric Rating Scale

CDSS: Calgary Depression Scale for Schizophrenia

CGI-I: Clinical Global Impression - Improvement Scale

CGI-S: Clinical Global Impression - Severity Scale

DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision

N: number of participants

PANSS: Positive and Negative Syndrome Scale

SD: standard deviation

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Lundbeck 2004	<p>Study 1</p> <p>Allocation: randomised.</p> <p>Participants: people with schizophrenia.</p> <p>Interventions: bifeprunox versus unknown active control.</p> <p>Outcomes: no data.</p> <p>Study 2</p> <p>Allocation: not described.</p>

Study	Reason for exclusion
	<p>Participants: people with schizophrenia.</p> <p>Interventions: bifeprunox versus unknown active control.</p> <p>Outcomes: no data.</p> <p>Study 3</p> <p>Allocation: not described.</p> <p>Participants: people with schizophrenia.</p> <p>Interventions: bifeprunox, no comparison stated.</p> <p>Outcomes: no data.</p> <p>Study 4</p> <p>Allocation: randomised.</p> <p>Participants: people with schizophrenia.</p> <p>Interventions: bifeprunox versus unknown active control.</p> <p>Outcomes: no data.</p> <p>Study 5</p> <p>Allocation: randomised.</p> <p>Participants: people with schizophrenia.</p> <p>Interventions: bifeprunox versus placebo.</p> <p>Outcomes: no data.</p> <p>Study 6</p> <p>Allocation: randomised.</p> <p>Participants: people with schizophrenia.</p> <p>Interventions: bifeprunox versus unknown active control.</p> <p>Outcomes: no data.</p> <p>Study 7</p> <p>Allocation: not described.</p> <p>Participants: people with schizophrenia.</p> <p>Interventions: bifeprunox, no comparison stated.</p> <p>Outcomes: no data.</p> <p>Unclear if all these short reports represent same study</p>
NCT00658645	<p>Allocation: randomised.</p> <p>Participants: people with schizophrenia.</p> <p>Interventions: bifeprunox versus placebo versus quetiapine.</p> <p>Outcomes: study terminated, no data.</p>

Study	Reason for exclusion
NCT00704509	Allocation: randomised. Participants: people with schizophrenia. Interventions: bifeprunox versus placebo versus quetiapine. Outcomes: study terminated, no data.

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

[NCT00139906](#)

Trial name or title	A randomized, double-blind, placebo-controlled, twice daily titration study of the safety and tolerability of bifeprunox in subjects with schizophrenia
Methods	Allocation: randomised. Blinding: double. Duration: 2 months. Design: parallel. Country: USA.
Participants	Diagnosis: schizophrenia. History: no information given. Sex: both included. Age: 18-55 years. Setting: no information given. Inclusion: current diagnosis of schizophrenia or schizoaffective disorder, weight of 100-250 lbs. Exclusion: acute psychosis, other Axis I diagnosis, significant suicide risk.
Interventions	1. Bifeprunox: dose maximum 40mg/day. 2. Placebo.
Outcomes	No data.
Starting date	August 2005.
Contact information	Solvay Pharmaceuticals. No further information.
Notes	No data currently published, hoping for future publications. Attempted contact but unable to gain further information.

NCT00139919

Trial name or title	A randomized, double-blind, placebo-controlled, sequential panel study of the safety and tolerability of progressively decreasing titration schedules of bifeprunox in subjects with either schizophrenia or bipolar disorder with an optional open-label 26-week extension study
Methods	Allocation: randomised. Blinding: double. Duration: 2 months with optional 26 week extension. Design: parallel. Country: USA.
Participants	Diagnosis: schizophrenia, bipolar type 1 (DSM-IV-TR) History: no information given. Sex: both included. Age: 18-55 years. Setting: no information given. Inclusion: current diagnosis of schizophrenia or bipolar disorder type 1, weight of 100-250 lbs, sufficient stability to allow discontinuation of antipsychotics. Exclusion: acute psychosis, acute mania, subjects with diagnosis other than bipolar type 1.
Interventions	1. Bifeprunox: dose maximum 40 mg/day. 2. Placebo.
Outcomes	No data.
Starting date	January 2006.
Contact information	staci.rockette@Solvay.com
Notes	No data currently published, hoping for future publications. Attempted contact but unable to gain further information.

DATA AND ANALYSES

Comparison 1. BIFEPRUNOX versus PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global state: 1. Deteriorated	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 20mg bifeprunox	1	231	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.54, 0.93]
1.2 30mg bifeprunox	1	241	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.46, 0.81]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Global state: 2. Mean change (CGI-S, bigger negative value = good)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 5mg bifeprunox	1	224	Mean Difference (IV, Random, 95% CI)	-0.33 [-0.59, -0.07]
2.2 10mg bifeprunox	1	232	Mean Difference (IV, Random, 95% CI)	0.07 [-0.17, 0.31]
2.3 20mg bifeprunox	2	549	Mean Difference (IV, Random, 95% CI)	-0.28 [-0.47, -0.10]
2.4 30mg bifeprunox	2	622	Mean Difference (IV, Random, 95% CI)	-0.25 [-0.44, -0.06]
2.5 40mg bifeprunox	1	285	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.36, 0.16]
3 Global state: 3. Mean end-point score (CGI-I, lower = good)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 5mg bifeprunox	1	224	Mean Difference (IV, Random, 95% CI)	-0.28 [-0.64, 0.08]
3.2 10mg bifeprunox	1	232	Mean Difference (IV, Random, 95% CI)	0.29 [-0.07, 0.65]
3.3 20mg bifeprunox	2	549	Mean Difference (IV, Random, 95% CI)	-0.41 [-0.81, -0.01]
3.4 30mg bifeprunox	1	338	Mean Difference (IV, Random, 95% CI)	-0.60 [-0.88, -0.32]
4 Mental state: 1. Mean change (PANSS total score, bigger negative value = good)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 5mg bifeprunox	1	224	Mean Difference (IV, Random, 95% CI)	-4.40 [-8.83, 0.03]
4.2 10mg bifeprunox	1	232	Mean Difference (IV, Random, 95% CI)	0.30 [-4.16, 4.76]
4.3 20mg bifeprunox	2	549	Mean Difference (IV, Random, 95% CI)	-7.03 [-9.98, -4.07]
4.4 30mg bifeprunox	1	338	Mean Difference (IV, Random, 95% CI)	-7.5 [-11.38, -3.62]
5 Mental state: 3. Mean change (PANSS negative subscale, bigger negative value = good)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 5mg bifeprunox	1	224	Mean Difference (IV, Random, 95% CI)	-0.90 [-2.15, 0.35]
5.2 10mg bifeprunox	1	232	Mean Difference (IV, Random, 95% CI)	-0.40 [-1.60, 0.80]
5.3 20mg bifeprunox	2	549	Mean Difference (IV, Random, 95% CI)	-1.53 [-2.37, -0.69]
5.4 30mg bifeprunox	2	622	Mean Difference (IV, Random, 95% CI)	-1.62 [-2.50, -0.73]
5.5 40mg bifeprunox	1	285	Mean Difference (IV, Random, 95% CI)	-0.40 [-1.68, 0.88]
6 Mental state: 2. Mean change (PANSS positive subscale, bigger negative value = good)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 5mg bifeprunox	1	224	Mean Difference (IV, Random, 95% CI)	-1.20 [-2.56, 0.16]
6.2 10mg bifeprunox	1	232	Mean Difference (IV, Random, 95% CI)	0.60 [-0.86, 2.06]
6.3 20mg bifeprunox	2	549	Mean Difference (IV, Random, 95% CI)	-1.89 [-2.85, -0.92]
6.4 30mg bifeprunox	2	622	Mean Difference (IV, Random, 95% CI)	-2.18 [-3.26, -1.10]
6.5 40mg bifeprunox	1	285	Mean Difference (IV, Random, 95% CI)	-1.70 [-3.43, 0.03]
7 Mental state: 4. Mean change (PANSS GPP subscale, bigger negative value = good)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 5mg bifeprunox	1	224	Mean Difference (IV, Random, 95% CI)	-2.40 [-4.76, -0.04]
7.2 10mg bifeprunox	1	232	Mean Difference (IV, Random, 95% CI)	0.0 [-2.29, 2.29]
7.3 20mg bifeprunox	2	549	Mean Difference (IV, Random, 95% CI)	-3.51 [-4.98, -2.03]
7.4 30mg bifeprunox	1	338	Mean Difference (IV, Random, 95% CI)	-3.40 [-5.34, -1.46]
8 Mental state: 5. Mean change (BPRS total score, bigger negative value = good)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 5mg bifeprunox	1	224	Mean Difference (IV, Random, 95% CI)	-2.40 [-5.12, 0.32]
8.2 10mg bifeprunox	1	232	Mean Difference (IV, Random, 95% CI)	0.40 [-2.41, 3.21]
8.3 20mg bifeprunox	2	549	Mean Difference (IV, Random, 95% CI)	-4.25 [-6.02, -2.48]
8.4 30mg bifeprunox	1	338	Mean Difference (IV, Random, 95% CI)	-4.0 [-6.22, -1.78]
9 Mental state: 6. Mean change (BPRS psychosis cluster, bigger negative value = good)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 5mg bifeprunox	1	224	Mean Difference (IV, Random, 95% CI)	-0.90 [-1.93, 0.13]
9.2 10mg bifeprunox	1	232	Mean Difference (IV, Random, 95% CI)	0.40 [-0.72, 1.52]
9.3 20mg bifeprunox	2	549	Mean Difference (IV, Random, 95% CI)	-1.25 [-1.78, -0.72]
9.4 30mg bifeprunox	1	338	Mean Difference (IV, Random, 95% CI)	-1.4 [-2.23, -0.57]
10 Mental state: 7. Mean change (CDSS total score, bigger negative value = good)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
10.1 20mg bifeprunox	1	324	Mean Difference (IV, Random, 95% CI)	-0.4 [-0.95, 0.15]
10.2 30mg bifeprunox	1	338	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.85, 0.25]
11 Leaving study early: 1. Total	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 5mg bifeprunox	1	234	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.78, 1.21]
11.2 10mg bifeprunox	1	239	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.89, 1.33]
11.3 20mg bifeprunox	3	863	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.75, 0.95]
11.4 30mg bifeprunox	3	935	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.79, 1.00]
11.5 40mg bifeprunox	1	297	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.78, 1.29]
12 Leaving study early: 2. Lack of efficacy	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 5mg bifeprunox	1	234	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.40, 1.18]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.2 10mg bifeprunox	1	239	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.83, 1.98]
12.3 20mg bifeprunox	3	863	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.53, 0.82]
12.4 30mg bifeprunox	3	935	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.45, 0.72]
12.5 40mg bifeprunox	1	297	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.44, 1.27]
13 Leaving study early: 3. Adverse event	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 5mg bifeprunox	1	234	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.41, 1.87]
13.2 10mg bifeprunox	1	239	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.44, 1.92]
13.3 20mg bifeprunox	3	863	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.64, 1.41]
13.4 30mg bifeprunox	3	935	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.47, 2.34]
13.5 40mg bifeprunox	1	297	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.35, 1.55]
14 Leaving study early: 4. Loss to follow-up	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
14.1 5mg bifeprunox	1	234	Risk Ratio (M-H, Random, 95% CI)	1.72 [0.65, 4.59]
14.2 10mg bifeprunox	1	239	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.19, 2.28]
14.3 20mg bifeprunox	3	863	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.39, 1.94]
14.4 30mg bifeprunox	3	935	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.61, 3.10]
14.5 40mg bifeprunox	1	297	Risk Ratio (M-H, Random, 95% CI)	3.69 [1.05, 12.96]
15 Leaving study early: 5. Protocol violation	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
15.1 5mg bifeprunox	1	234	Risk Ratio (M-H, Random, 95% CI)	1.55 [0.26, 9.12]
15.2 10mg bifeprunox	1	239	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.25, 8.74]
15.3 20mg bifeprunox	3	863	Risk Ratio (M-H, Random, 95% CI)	1.90 [0.69, 5.24]
15.4 30mg bifeprunox	3	935	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.45, 2.20]
15.5 40mg bifeprunox	1	297	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.23, 2.21]
16 Leaving study early: 6. Withdrew consent	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
16.1 5mg bifeprunox	1	234	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.70, 2.00]
16.2 10mg bifeprunox	1	239	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.57, 1.72]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.3 20mg bifeprunox	3	863	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.65, 1.35]
16.4 30mg bifeprunox	3	935	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.81, 1.70]
16.5 40mg bifeprunox	1	297	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.64, 2.23]
17 Leaving study early: 7. Other	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
17.1 5mg bifeprunox	1	234	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.38]
17.2 10mg bifeprunox	1	239	Risk Ratio (M-H, Random, 95% CI)	1.98 [0.18, 21.58]
17.3 20mg bifeprunox	2	559	Risk Ratio (M-H, Random, 95% CI)	2.85 [0.53, 15.40]
17.4 30mg bifeprunox	1	338	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.84]
18 Adverse effects: 1. Total	2	1369	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.98, 1.29]
18.1 5mg bifeprunox	1	234	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.95, 1.15]
18.2 10mg bifeprunox	1	239	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.92, 1.13]
18.3 20mg bifeprunox	2	558	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.85, 1.42]
18.4 30mg bifeprunox	1	338	Risk Ratio (M-H, Random, 95% CI)	1.44 [1.24, 1.66]
19 Adverse effects: 2. Gastrointestinal: i. Constipation	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
19.1 5mg bifeprunox	1	234	Risk Ratio (M-H, Random, 95% CI)	1.51 [0.73, 3.10]
19.2 10mg bifeprunox	1	239	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.30, 1.73]
19.3 20mg bifeprunox	2	536	Risk Ratio (M-H, Random, 95% CI)	2.71 [1.30, 5.67]
19.4 30mg bifeprunox	2	593	Risk Ratio (M-H, Random, 95% CI)	2.78 [1.50, 5.14]
19.5 40mg bifeprunox	1	296	Risk Ratio (M-H, Random, 95% CI)	2.15 [0.96, 4.84]
20 Adverse effects: 2. Gastrointestinal: ii. Dyspepsia	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
20.1 5mg bifeprunox	1	234	Risk Ratio (M-H, Random, 95% CI)	2.48 [1.24, 4.96]
20.2 10mg bifeprunox	1	239	Risk Ratio (M-H, Random, 95% CI)	2.28 [1.14, 4.58]
20.3 20mg bifeprunox	1	233	Risk Ratio (M-H, Random, 95% CI)	1.88 [0.91, 3.90]
20.4 30mg bifeprunox	1	294	Risk Ratio (M-H, Random, 95% CI)	2.35 [1.00, 5.54]
20.5 40mg bifeprunox	1	296	Risk Ratio (M-H, Random, 95% CI)	2.03 [0.84, 4.88]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21 Adverse effects: 2. Gastrointestinal: iii. GI upset	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
21.1 5mg bifeprunox	1	234	Risk Ratio (M-H, Random, 95% CI)	10.35 [1.35, 79.55]
21.2 10mg bifeprunox	1	239	Risk Ratio (M-H, Random, 95% CI)	12.89 [1.71, 97.00]
21.3 20mg bifeprunox	1	233	Risk Ratio (M-H, Random, 95% CI)	4.18 [0.47, 36.80]
22 Adverse effects: 2. Gastrointestinal: iv. Nausea	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
22.1 5mg bifeprunox	1	234	Risk Ratio (M-H, Random, 95% CI)	1.98 [1.00, 3.91]
22.2 10mg bifeprunox	1	239	Risk Ratio (M-H, Random, 95% CI)	1.80 [0.90, 3.60]
22.3 20mg bifeprunox	3	861	Risk Ratio (M-H, Random, 95% CI)	2.51 [1.34, 4.68]
22.4 30mg bifeprunox	3	931	Risk Ratio (M-H, Random, 95% CI)	3.41 [1.65, 7.01]
22.5 40mg bifeprunox	1	296	Risk Ratio (M-H, Random, 95% CI)	3.72 [1.84, 7.49]
23 Adverse effects: 2. Gastrointestinal: v. Vomiting	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
23.1 5mg bifeprunox	1	234	Risk Ratio (M-H, Random, 95% CI)	2.07 [0.92, 4.65]
23.2 10mg bifeprunox	1	239	Risk Ratio (M-H, Random, 95% CI)	2.36 [1.07, 5.17]
23.3 20mg bifeprunox	3	861	Risk Ratio (M-H, Random, 95% CI)	3.14 [1.86, 5.29]
23.4 30mg bifeprunox	3	931	Risk Ratio (M-H, Random, 95% CI)	2.34 [1.26, 4.35]
23.5 40mg bifeprunox	1	296	Risk Ratio (M-H, Random, 95% CI)	2.03 [1.08, 3.79]
24 Adverse effects: 2. Gastrointestinal: vi. Diarrhoea	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
24.1 30mg bifeprunox	1	294	Risk Ratio (M-H, Random, 95% CI)	9.25 [1.19, 72.08]
24.2 40mg bifeprunox	1	296	Risk Ratio (M-H, Random, 95% CI)	9.12 [1.17, 71.10]
25 Adverse effects: 3. Psychiatric: i. Anxiety	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
25.1 5mg bifeprunox	1	234	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.34, 3.12]
25.2 10mg bifeprunox	1	239	Risk Ratio (M-H, Random, 95% CI)	1.98 [0.77, 5.11]
25.3 20mg bifeprunox	1	233	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.42, 3.51]
25.4 30mg bifeprunox	1	294	Risk Ratio (M-H, Random, 95% CI)	1.85 [0.64, 5.39]
25.5 40mg bifeprunox	1	296	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.38, 3.90]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
26 Adverse effects: 3. Psychiatric: ii. Psychosis aggravated	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
26.1 5mg bifeprunox	1	234	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.20, 2.38]
26.2 10mg bifeprunox	1	239	Risk Ratio (M-H, Random, 95% CI)	1.98 [0.77, 5.11]
26.3 20mg bifeprunox	1	233	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.27, 2.77]
27 Adverse effects: 3. Psychiatric: iii. Schizophrenia aggravated	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
27.1 5mg bifeprunox	1	234	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.42, 3.48]
27.2 10mg bifeprunox	1	239	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.26, 2.63]
27.3 20mg bifeprunox	1	233	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.50, 3.89]
28 Adverse effects: 4. Extrapyramidal side effects: i. Extrapyramidal disorder	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
28.1 30mg bifeprunox	1	294	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.33, 2.42]
28.2 40mg bifeprunox	1	296	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.39, 2.63]
29 Adverse effects: 4. Extrapyramidal side effects: ii. Tremor	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
29.1 30mg bifeprunox	1	294	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.51, 3.45]
29.2 40mg bifeprunox	1	296	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.57, 3.70]
30 Adverse effects: 4. Extrapyramidal side effects: iii. Akathisia	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
30.1 5mg bifeprunox	1	234	Risk Ratio (M-H, Random, 95% CI)	3.10 [0.13, 75.41]
30.2 10mg bifeprunox	1	239	Risk Ratio (M-H, Random, 95% CI)	4.96 [0.24, 102.21]
30.3 20mg bifeprunox	2	558	Risk Ratio (M-H, Random, 95% CI)	6.03 [1.59, 22.82]
30.4 30mg bifeprunox	2	632	Risk Ratio (M-H, Random, 95% CI)	1.83 [0.50, 6.69]
30.5 40mg bifeprunox	1	296	Risk Ratio (M-H, Random, 95% CI)	2.03 [0.71, 5.79]
31 Adverse effects: 4. Extrapyramidal side effects: iv. Bradykinesia	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
31.1 30mg bifeprunox	1	294	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
31.2 40mg bifeprunox	1	296	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
32 Adverse effects: 4. Extrapyramidal side effects: v. Choreoathetosis	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
32.1 30mg bifeprunox	1	294	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
32.2 40mg bifeprunox	1	296	Risk Ratio (M-H, Random, 95% CI)	3.04 [0.12, 74.04]
33 Adverse effects: 4. Extrapyramidal side effects: vi. Cogwheel rigidity	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
33.1 30mg bifeprunox	1	294	Risk Ratio (M-H, Random, 95% CI)	3.08 [0.13, 75.05]
33.2 40mg bifeprunox	1	296	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
34 Adverse effects: 4. Extrapyramidal side effects: vii. Dyskinesia	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
34.1 20mg bifeprunox	1	325	Risk Ratio (M-H, Random, 95% CI)	2.09 [0.19, 22.80]
34.2 30mg bifeprunox	2	632	Risk Ratio (M-H, Random, 95% CI)	8.47 [1.56, 45.87]
34.3 40mg bifeprunox	1	296	Risk Ratio (M-H, Random, 95% CI)	9.12 [0.50, 167.93]
35 Adverse effects: 4. Extrapyramidal side effects: viii. Dystonia	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
35.1 30mg bifeprunox	1	294	Risk Ratio (M-H, Random, 95% CI)	3.08 [0.32, 29.30]
35.2 40mg bifeprunox	1	296	Risk Ratio (M-H, Random, 95% CI)	3.04 [0.32, 28.90]
36 Adverse effects: 4. Extrapyramidal side effects: ix. Parkinsonism	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
36.1 30mg bifeprunox	1	294	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
36.2 40mg bifeprunox	1	296	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
37 Adverse effects: 4. Extrapyramidal side effects: x. Tardive dyskinesia	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
37.1 30mg bifeprunox	1	294	Risk Ratio (M-H, Random, 95% CI)	5.14 [0.25, 106.09]
37.2 40mg bifeprunox	1	296	Risk Ratio (M-H, Random, 95% CI)	3.04 [0.12, 74.04]
38 Adverse effects: 5. Lipid profile: i. Mean change (Total	2		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
cholesterol, bigger negative value = good)				
38.1 20mg bifeprunox	1	259	Mean Difference (IV, Random, 95% CI)	-3.60 [-11.18, 3.98]
38.2 30mg bifeprunox	1	255	Mean Difference (IV, Random, 95% CI)	-3.80 [-12.14, 4.54]
38.3 Bifeprunox total	1	260	Mean Difference (IV, Random, 95% CI)	-8.9 [-16.29, -1.51]
39 Adverse effects: 5. Lipid profile: ii. Mean change (Triglycerides, bigger negative value = good)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
39.1 20mg bifeprunox	1	259	Mean Difference (IV, Random, 95% CI)	3.0 [-20.18, 26.18]
39.2 30mg bifeprunox	1	255	Mean Difference (IV, Random, 95% CI)	-23.6 [-47.02, -0.18]
39.3 Bifeprunox total	1	260	Mean Difference (IV, Random, 95% CI)	-23.8 [-41.15, -6.45]
40 Adverse effects: 5. Lipid profile: iii. Mean change (VLDL, bigger negative value = good)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
40.1 20mg bifeprunox	1	259	Mean Difference (IV, Random, 95% CI)	0.60 [-3.28, 4.48]
40.2 30mg bifeprunox	1	255	Mean Difference (IV, Random, 95% CI)	-2.80 [-6.58, 0.98]
41 Adverse effects: 5. Lipid profile: iv. Mean change (LDL, bigger negative value = good)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
41.1 20mg bifeprunox	1	259	Mean Difference (IV, Random, 95% CI)	0.60 [-6.60, 7.80]
41.2 30mg bifeprunox	1	255	Mean Difference (IV, Random, 95% CI)	1.20 [-6.18, 8.58]
41.3 Bifeprunox total	1	252	Mean Difference (IV, Random, 95% CI)	-6.6 [-13.07, -0.13]
42 Adverse effects: 5. Lipid profile: v. Mean change (HDL, bigger negative value = bad)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
42.1 20mg bifeprunox	1	259	Mean Difference (IV, Random, 95% CI)	-1.70 [-4.88, 1.48]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
42.2 30mg bifeprunox	1	255	Mean Difference (IV, Random, 95% CI)	0.20 [-3.18, 3.58]
42.3 Bifeprunox total	1	260	Mean Difference (IV, Random, 95% CI)	1.7 [-1.24, 4.64]
43 Adverse effects: 5. Lipid profile: vi. TG:HDL ratio (bigger negative value = good)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
44 Adverse effects: 6. Weight: i. Mean change (kg, bigger positive value = bad)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
45 Adverse effects: 6. Weight: ii. Total number of participants with $\geq 7\%$ weight increase	1	483	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.31, 3.33]
46 Adverse effects: 6. Weight: iii. Total number of participants with $\geq 7\%$ weight decrease	1	483	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.66, 2.54]
47 Adverse effects: 6. Weight iv. Appetite decrease	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
47.1 5mg bifeprunox	1	234	Risk Ratio (M-H, Random, 95% CI)	3.62 [0.77, 17.07]
47.2 10mg bifeprunox	1	239	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.05, 5.40]
47.3 20mg bifeprunox	1	233	Risk Ratio (M-H, Random, 95% CI)	3.13 [0.65, 15.20]
47.4 30mg bifeprunox	1	294	Risk Ratio (M-H, Random, 95% CI)	3.43 [0.96, 12.19]
47.5 40mg bifeprunox	1	296	Risk Ratio (M-H, Random, 95% CI)	2.70 [0.73, 9.99]
48 Adverse effects: 6. Weight: v. Anorexia	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
48.1 20mg bifeprunox	1	325	Risk Ratio (M-H, Random, 95% CI)	19.83 [1.16, 337.92]
48.2 30mg bifeprunox	2	632	Risk Ratio (M-H, Random, 95% CI)	10.03 [1.08, 92.99]
48.3 40mg bifeprunox	1	296	Risk Ratio (M-H, Random, 95% CI)	9.12 [1.17, 71.10]
49 Adverse effects: 7. Pain: i. General pain	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
49.1 5mg bifeprunox	1	234	Risk Ratio (M-H, Random, 95% CI)	3.10 [0.86, 11.18]
49.2 10mg bifeprunox	1	239	Risk Ratio (M-H, Random, 95% CI)	1.65 [0.40, 6.76]
49.3 20mg bifeprunox	2	536	Risk Ratio (M-H, Random, 95% CI)	1.97 [0.74, 5.23]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
49.4 30mg bifeprunox	1	299	Risk Ratio (M-H, Random, 95% CI)	1.66 [0.40, 6.80]
50 Adverse effects: 7. Pain: ii. Back pain	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
50.1 20mg bifeprunox	1	303	Risk Ratio (M-H, Random, 95% CI)	3.87 [0.84, 17.93]
50.2 30mg bifeprunox	1	299	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.05, 5.42]
51 Adverse effects: 7. Pain: iii. Arthralgia	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
51.1 20mg bifeprunox	1	303	Risk Ratio (M-H, Random, 95% CI)	6.77 [0.84, 54.38]
51.2 30mg bifeprunox	1	299	Risk Ratio (M-H, Random, 95% CI)	2.98 [0.31, 28.32]
52 Adverse effect: 8. Other: i. Asthenia	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
52.1 20mg bifeprunox	1	325	Risk Ratio (M-H, Random, 95% CI)	11.48 [0.64, 205.95]
52.2 30mg bifeprunox	1	338	Risk Ratio (M-H, Random, 95% CI)	18.34 [1.08, 312.62]
53 Adverse effects: 8. Other: ii. Dysmenorrhoea	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
53.1 5mg bifeprunox	1	234	Risk Ratio (M-H, Random, 95% CI)	3.10 [0.13, 75.41]
53.2 10mg bifeprunox	1	239	Risk Ratio (M-H, Random, 95% CI)	4.96 [0.24, 102.21]
53.3 20mg bifeprunox	1	233	Risk Ratio (M-H, Random, 95% CI)	3.13 [0.13, 76.06]
54 Adverse effects: 8. Other: iii. Dry mouth	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
54.1 20mg bifeprunox	1	303	Risk Ratio (M-H, Random, 95% CI)	2.58 [0.70, 9.54]
54.2 30mg bifeprunox	2	593	Risk Ratio (M-H, Random, 95% CI)	2.17 [0.66, 7.09]
54.3 40mg bifeprunox	1	296	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.06, 16.05]
55 Adverse effects: 8. Other: iv. Fatigue	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
55.1 30mg bifeprunox	1	294	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.04, 3.26]
55.2 40mg bifeprunox	1	296	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.21, 4.94]
56 Adverse effects: 8. Other: v. Vaginitis	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
56.1 30mg bifeprunox	1	294	Risk Ratio (M-H, Random, 95% CI)	5.14 [0.25, 106.09]
56.2 40mg bifeprunox	1	296	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
57 Adverse effects: 8. Other: vi. Dizziness	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
57.1 20mg bifeprunox	1	325	Risk Ratio (M-H, Random, 95% CI)	1.74 [0.42, 7.16]
57.2 30mg bifeprunox	2	632	Risk Ratio (M-H, Random, 95% CI)	3.02 [1.05, 8.62]
57.3 40mg bifeprunox	1	296	Risk Ratio (M-H, Random, 95% CI)	3.38 [1.40, 8.17]
58 Adverse effects: 8. Other: vii. Somnolence	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
58.1 20mg bifeprunox	1	303	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.22, 2.13]
58.2 30mg bifeprunox	1	299	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.17, 1.90]
59 Adverse effects: 8. Other: vii. Sedation	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
59.1 20mg bifeprunox	1	303	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.46, 3.63]
59.2 30mg bifeprunox	2	593	Risk Ratio (M-H, Random, 95% CI)	2.07 [0.90, 4.76]
59.3 40mg bifeprunox	1	296	Risk Ratio (M-H, Random, 95% CI)	2.03 [0.38, 10.90]
60 Adverse effects: 8. Other: ix. Nasopharyngitis	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
60.1 20mg bifeprunox	1	303	Risk Ratio (M-H, Random, 95% CI)	2.26 [0.59, 8.57]
60.2 30mg bifeprunox	1	299	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.30, 5.82]

Analysis 1.1. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 1 Global state: 1. Deteriorated.

Analysis 1.2. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 2 Global state: 2. Mean change (CGI-S, bigger negative value = good).

Analysis 1.3. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 3 Global state: 3. Mean endpoint score (CGI-I, lower = good).

Analysis 1.4. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 4 Mental state: 1. Mean change (PANSS total score, bigger negative value = good).

Analysis 1.5. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 5 Mental state: 3. Mean change (PANSS negative subscale, bigger negative value = good).

Analysis 1.6. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 6 Mental state: 2. Mean change (PANSS positive subscale, bigger negative value = good).

Analysis 1.7. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 7 Mental state: 4. Mean change (PANSS GPP subscale, bigger negative value = good).

Analysis 1.8. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 8 Mental state: 5. Mean change (BPRS total score, bigger negative value = good).

Analysis 1.9. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 9 Mental state: 6. Mean change (BPRS psychosis cluster, bigger negative value = good).

Analysis 1.10. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 10 Mental state: 7. Mean change (CDSS total score, bigger negative value = good).

Analysis 1.11. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 11 Leaving study early: 1. Total.

Analysis 1.12. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 12 Leaving study early: 2. Lack of efficacy.

Analysis 1.13. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 13 Leaving study early: 3. Adverse event.

Analysis 1.14. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 14 Leaving study early: 4. Loss to follow-up.

Analysis 1.15. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 15 Leaving study early: 5. Protocol violation.

Analysis 1.16. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 16 Leaving study early: 6. Withdrew consent.

Analysis 1.17. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 17 Leaving study early: 7. Other.

Analysis 1.18. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 18 Adverse effects: 1. Total.

Analysis 1.19. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 19 Adverse effects: 2. Gastrointestinal: i. Constipation.

Analysis 1.20. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 20 Adverse effects: 2. Gastrointestinal: ii. Dyspepsia.

Analysis 1.21. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 21 Adverse effects: 2. Gastrointestinal: iii. GI upset.

Analysis 1.22. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 22 Adverse effects: 2. Gastrointestinal: iv. Nausea.

Analysis 1.23. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 23 Adverse effects: 2. Gastrointestinal: v. Vomiting.

Analysis 1.24. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 24 Adverse effects: 2. Gastrointestinal: vi. Diarrhoea.

Analysis 1.25. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 25 Adverse effects: 3. Psychiatric: i. Anxiety.

Analysis 1.26. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 26 Adverse effects: 3. Psychiatric: ii. Psychosis aggravated.

Study or subgroup	Bifeprunox n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for subgroup differences: $\chi^2=2.14$, $df=1$ ($P=0.34$), $I^2=6.68\%$					
Favours bifeprunox 0.01 0.1 1 10 100 Favours placebo					

Analysis 1.27. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 27 Adverse effects: 3. Psychiatric: iii. Schizophrenia aggravated.

Study or subgroup	Bifeprunox n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.27.1 5mg bifeprunox					
Casey 2007	7/115	6/119		100%	1.21[0.42,3.48]
Subtotal (95% CI)	115	119		100%	1.21[0.42,3.48]
Total events: 7 (Bifeprunox), 6 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: $Z=0.35$ ($P=0.73$)					
1.27.2 10mg bifeprunox					
Casey 2007	5/120	6/119		100%	0.83[0.26,2.63]
Subtotal (95% CI)	120	119		100%	0.83[0.26,2.63]
Total events: 5 (Bifeprunox), 6 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: $Z=0.32$ ($P=0.75$)					
1.27.3 20mg bifeprunox					
Casey 2007	8/114	6/119		100%	1.39[0.5,3.89]
Subtotal (95% CI)	114	119		100%	1.39[0.5,3.89]
Total events: 8 (Bifeprunox), 6 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: $Z=0.63$ ($P=0.53$)					
Test for subgroup differences: $\chi^2=0.45$, $df=1$ ($P=0.8$), $I^2=0\%$					
Favours bifeprunox 0.01 0.1 1 10 100 Favours placebo					

Analysis 1.28. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 28 Adverse effects: 4. Extrapyramidal side effects: i. Extrapyramidal disorder.

Study or subgroup	Bifeprunox n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.28.1 30mg bifeprunox					
Meltzer 2007	7/145	8/149		100%	0.9[0.33,2.42]
Subtotal (95% CI)	145	149		100%	0.9[0.33,2.42]
Total events: 7 (Bifeprunox), 8 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: $Z=0.21$ ($P=0.83$)					
1.28.2 40mg bifeprunox					
Meltzer 2007	8/147	8/149		100%	1.01[0.39,2.63]
Subtotal (95% CI)	147	149		100%	1.01[0.39,2.63]
Total events: 8 (Bifeprunox), 8 (Placebo)					
Favours bifeprunox 0.01 0.1 1 10 100 Favours placebo

Analysis 1.29. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 29 Adverse effects: 4. Extrapyramidal side effects: ii. Tremor.

Analysis 1.30. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 30 Adverse effects: 4. Extrapyramidal side effects: iii. Akathisia.

Analysis 1.31. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 31 Adverse effects: 4. Extrapyramidal side effects: iv. Bradykinesia.

Analysis 1.32. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 32 Adverse effects: 4. Extrapyramidal side effects: v. Choreaethetosis.

Analysis 1.33. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 33 Adverse effects: 4. Extrapyramidal side effects: vi. Cogwheel rigidity.

Analysis 1.34. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 34 Adverse effects: 4. Extrapyramidal side effects: vii. Dyskinesia.

Analysis 1.35. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 35 Adverse effects: 4. Extrapyramidal side effects: viii. Dystonia.

Analysis 1.36. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 36 Adverse effects: 4. Extrapyramidal side effects: ix. Parkinsonism.

Analysis 1.37. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 37 Adverse effects: 4. Extrapyramidal side effects: x. Tardive dyskinesia.

Analysis 1.38. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 38 Adverse effects: 5. Lipid profile: i. Mean change (Total cholesterol, bigger negative value = good).

Analysis 1.39. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 39 Adverse effects: 5. Lipid profile: ii. Mean change (Triglycerides, bigger negative value = good).

Analysis 1.40. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 40 Adverse effects: 5. Lipid profile: iii. Mean change (VLDL, bigger negative value = good).

Analysis 1.41. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 41 Adverse effects: 5. Lipid profile: iv. Mean change (LDL, bigger negative value = good).

Analysis 1.42. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 42 Adverse effects: 5. Lipid profile: v. Mean change (HDL, bigger negative value = bad).

Analysis 1.43. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 43 Adverse effects: 5. Lipid profile: vi. TG:HDL ratio (bigger negative value = good).

Analysis 1.44. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 44 Adverse effects: 6. Weight: i. Mean change (kg, bigger positive value = bad).

Analysis 1.45. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 45 Adverse effects: 6. Weight: ii. Total number of participants with ≥ 7% weight increase.

Analysis 1.46. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 46 Adverse effects: 6. Weight: iii. Total number of participants with $\geq 7\%$ weight decrease.

Analysis 1.47. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 47 Adverse effects: 6. Weight iv. Appetite decrease.

Analysis 1.48. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 48 Adverse effects: 6. Weight: v. Anorexia.

Analysis 1.49. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 49 Adverse effects: 7. Pain: i. General pain.

Analysis 1.50. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 50 Adverse effects: 7. Pain: ii. Back pain.

Study or subgroup	Bifeprunox n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for subgroup differences: $\chi^2=2.01$, $df=1$ ($P=0.16$), $I^2=50.22\%$					
Favours bifeprunox 0.01 0.1 1 10 100 Favours placebo					

Analysis 1.51. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 51 Adverse effects: 7. Pain: iii. Arthralgia.

Study or subgroup	Bifeprunox n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.51.1 20mg bifeprunox					
Barbato 2006	7/154	1/149		100%	6.77[0.84,54.38]
Subtotal (95% CI)	154	149		100%	6.77[0.84,54.38]
Total events: 7 (Bifeprunox), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: $Z=1.8$ ($P=0.07$)					
1.51.2 30mg bifeprunox					
Barbato 2006	3/150	1/149		100%	2.98[0.31,28.32]
Subtotal (95% CI)	150	149		100%	2.98[0.31,28.32]
Total events: 3 (Bifeprunox), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: $Z=0.95$ ($P=0.34$)					
Test for subgroup differences: $\chi^2=0.28$, $df=1$ ($P=0.6$), $I^2=0\%$					
Favours bifeprunox 0.01 0.1 1 10 100 Favours placebo					

Analysis 1.52. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 52 Adverse effect: 8. Other: i. Asthenia.

Study or subgroup	Bifeprunox n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.52.1 20mg bifeprunox					
Bourin 2007	5/159	0/166		100%	11.48[0.64,205.95]
Subtotal (95% CI)	159	166		100%	11.48[0.64,205.95]
Total events: 5 (Bifeprunox), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: $Z=1.66$ ($P=0.1$)					
1.52.2 30mg bifeprunox					
Bourin 2007	9/172	0/166		100%	18.34[1.08,312.62]
Subtotal (95% CI)	172	166		100%	18.34[1.08,312.62]
Total events: 9 (Bifeprunox), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: $Z=2.01$ ($P=0.04$)					
Test for subgroup differences: $\chi^2=0.05$, $df=1$ ($P=0.82$), $I^2=0\%$					
Favours bifeprunox 0.02 0.1 1 10 50 Favours placebo					

**Analysis 1.53. Comparison 1 BIFEPRUNOX versus PLACEBO,
Outcome 53 Adverse effects: 8. Other: ii: Dysmenorrhoea.**

Analysis 1.54. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 54 Adverse effects: 8. Other: iii. Dry mouth.

Study or subgroup	Bifeprunox n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: $Z=0.01(P=0.99)$					
Test for subgroup differences: $\chi^2=0.36$, $df=1$ ($P=0.84$), $I^2=0\%$

Analysis 1.55. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 55 Adverse effects: 8. Other: iv. Fatigue.

Study or subgroup	Bifeprunox n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.55.1 30mg bifeprunox					
Meltzer 2007	1/145	3/149		100%	0.34[0.04,3.26]
Subtotal (95% CI)	145	149		100%	0.34[0.04,3.26]
Total events: 1 (Bifeprunox), 3 (Placebo)					
Heterogeneity: $\tau^2=0$; $\chi^2=0$, $df=0$ ($P<0.0001$); $I^2=100\%$					
Test for overall effect: $Z=0.93(P=0.35)$					
1.55.2 40mg bifeprunox					
Meltzer 2007	3/147	3/149		100%	1.01[0.21,4.94]
Subtotal (95% CI)	147	149		100%	1.01[0.21,4.94]
Total events: 3 (Bifeprunox), 3 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: $Z=0.02(P=0.99)$					
Test for subgroup differences: $\chi^2=0.6$, $df=1$ ($P=0.44$), $I^2=0\%$

Analysis 1.56. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 56 Adverse effects: 8. Other: v. Vaginitis.

Study or subgroup	Bifeprunox n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.56.1 30mg bifeprunox					
Meltzer 2007	2/145	0/149		100%	5.14[0.25,106.09]
Subtotal (95% CI)	145	149		100%	5.14[0.25,106.09]
Total events: 2 (Bifeprunox), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: $Z=1.06(P=0.29)$					
1.56.2 40mg bifeprunox					
Meltzer 2007	0/147	0/149			Not estimable
Subtotal (95% CI)	147	149			Not estimable
Total events: 0 (Bifeprunox), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Not applicable

Analysis 1.57. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 57 Adverse effects: 8. Other: vi. Dizziness.

Analysis 1.58. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 58 Adverse effects: 8. Other: vii. Somnolence.

Analysis 1.59. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 59 Adverse effects: 8. Other: viii. Sedation.

Analysis 1.60. Comparison 1 BIFEPRUNOX versus PLACEBO, Outcome 60 Adverse effects: 8. Other: ix. Nasopharyngitis.

ADDITIONAL TABLES

Bifeprunox versus placebo for schizophrenia (Review)

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Table 1. Other comparisons relevant to trials in this review

Comparison	Trial	Existing review
Quetiapine versus placebo	NCT00658645 ; NCT00704509	Lankappa 2012
Olanzapine versus placebo	Barbato 2006 ; Bourin 2007	Duggan 2005
Risperidone versus placebo	Bourin 2007 ; Casey 2007 ; Meltzer 2007	Ratthalli 2010
Haloperidol versus placebo	Bourin 2007	Adams 2013
Olanzapine versus risperidone	Bourin 2007	Jayaram 2006
Haloperidol versus olanzapine	Bourin 2007	Duggan 2005
Haloperidol versus risperidone	Bourin 2007	Hunter 2003

Table 2. Timeline

Trial	Date	Event	Link
	2004	Participant dies in multicentre bifeprunox trial in Bulgaria. Autopsy report said cause was unclear (but "possibly cardiovascular and exogenous factors")	Figure 3
Barbato 2006			
Bourin 2007 , Casey 2007 , Meltzer 2007	2007	Patient "R" speaks of harrowing experience in a bifeprunox trial in Minnesota. Felt coerced and described how the trial co-ordinator dismissed his abdominal pain concerns as "unlikely" to be related to bifeprunox	Ballion 2014
	August 2007	FDA does not approve bifeprunox. Efficacy data when compared to reference drugs not sufficient. More data needed about human metabolism - especially on participant who died in 2004. Report claims bifeprunox approval key to Solvay's future	Beaulieu 2007
	October 2007	Solvay and partners send investigators to Bulgaria; documents and samples obtained. Reviewed and concluded that participant died due to steatosis, metabolic abnormalities, renal dysfunction, and coma originating from a toxic reaction to the drug	Figure 4
	December 2007	Solvay suspends all trials	Figure 5
	July 2009	Lundbeck and Solvay announce termination of all research relating to bifeprunox	Kronborg 2009
	September	Solvay sells pharmaceutical division to Abbott Labs	Gray-Block 2009

Table 2. Timeline (Continued)
2009

May 2015	An independent consultant reviewed that Patient 'R' was not given timely info re safety issues.	Olson 2015
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Table 3. Design of a future study

Methods	Allocation: centralised sequence generation with table of random numbers or computer-generated code, stratified by severity of illness, sequence concealed until interventions assigned. Blinding: those recruiting and assigning participants and those assessing outcomes, all blind to allocated group, blinding could be tested. Duration: 6 months.
Participants	Diagnosis: schizophrenia, if operational criteria used these should be in the context of routine care. N = 450*. Age: adults. Sex: men and women. Setting: Both hospital and outpatients, across a variety of countries.
Interventions	1. Bifeprunox 20mg, once daily dose. N = 150. 2. Bifeprunox 30mg, once daily dose. N = 150. 3. Placebo pill. N = 150. This will be indistinguishable from bifeprunox pills.
Outcomes	Mental state: PANSS positive and negative sub-scales** Service outcomes: re-hospitalisation, days in hospital, time attending psychiatric outpatient clinic. Global state: CGI-I and CGI-S Quality of life: important change. Adverse effects: including mortality, weight change and extrapyramidal symptoms. Satisfaction with care: patients/carers. Economic data. Other routine data, such as incidents with the police.
Notes	* size of study to detect a 10% difference in improvement with 80% certainty. ** primary outcome. For all outcomes there should be binary cut off points of clinically important improvement, defined before the study starts

BPRS: Brief Psychiatric Rating Scale
CGI-I: Clinical Global Impression - Improvement Scale
CGI-S: Clinical Global Impression - Severity Scale
N: number of participants
PANSS: Positive and Negative Syndrome Scale

CONTRIBUTIONS OF AUTHORS

All review authors contributed to the writing and development of the protocol.

AC: writing and development.
SF: writing and development.
GG: writing and development.

SF and GG contributed to data extraction and initial work on the results.

AC re-extracted the data, rewrote the results, and wrote the conclusion.

DECLARATIONS OF INTEREST

AC: none known.

SF: none known.

GG: none known.

SOURCES OF SUPPORT

Internal sources

- University of Nottingham, UK.

Students at University of Nottingham

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Antipsychotic Agents [adverse effects] [*therapeutic use]; Benzoxazoles [adverse effects] [*therapeutic use]; Drug Approval; Intention to Treat Analysis; Piperazines [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic; Schizophrenia [*drug therapy]; Schizophrenic Psychology; United States; United States Food and Drug Administration

MeSH check words

Humans