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Pharmacological interventions for benzodiazepine discontinuation in chronic benzodiazepine users (Review)

Baandrup L, Ebdrup BH, Rasmussen JØ, Lindschou J, Gluud C, Glenthøj BY

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[Intervention Review]

Pharmacological interventions for benzodiazepine discontinuation in chronic benzodiazepine users

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ABSTRACT

Background

Prolonged treatment with benzodiazepines is common practice despite clinical recommendations of short-term use. Benzodiazepines are used by approximately 4% of the general population, with increased prevalence in psychiatric populations and the elderly. After long-term use it is often difficult to discontinue benzodiazepines due to psychological and physiological dependence. This review investigated if pharmacological interventions can facilitate benzodiazepine tapering.

Objectives

To assess the benefits and harms of pharmacological interventions to facilitate discontinuation of chronic benzodiazepine use.

Search methods

We searched the following electronic databases up to October 2017: Cochrane Drugs and Alcohol Group's Specialised Register of Trials, CENTRAL, PubMed, Embase, CINAHL, and ISI Web of Science. We also searched ClinicalTrials.gov, the WHO ICTRP, and ISRCTN registry, and checked the reference lists of included studies for further references to relevant randomised controlled trials.

Selection criteria

We included randomised controlled trials comparing pharmacological treatment versus placebo or no intervention or versus another pharmacological intervention in adults who had been treated with benzodiazepines for at least two months and/or fulfilled criteria for benzodiazepine dependence (any criteria).

Data collection and analysis

We used standard methodological procedures expected by Cochrane.

Main results

We included 38 trials (involving 2543 participants), but we could only extract data from 35 trials with 2295 participants. Many different interventions were studied, and no single intervention was assessed in more than four trials. We extracted data on 18 different comparisons. The risk of bias was high in all trials but one. Trial Sequential Analysis showed imprecision for all comparisons.

For benzodiazepine discontinuation, we found a potential benefit of valproate at end of intervention (1 study, 27 participants; risk ratio (RR) 2.55, 95% confidence interval (CI) 1.08 to 6.03; very low-quality evidence) and of tricyclic antidepressants at longest follow-up (1 study, 47 participants; RR 2.20, 95% CI 1.27 to 3.82; low-quality evidence).

We found potentially positive effects on benzodiazepine withdrawal symptoms of pregabalin (1 study, 106 participants; mean difference (MD) -3.10 points, 95% CI -3.51 to -2.69; very low-quality evidence), captodiame (1 study, 81 participants; MD -1.00 points, 95% CI -1.13 to -0.87; very low-quality evidence), paroxetine (2 studies, 99 participants; MD -3.57 points, 95% CI -5.34 to -1.80; very low-quality evidence), tricyclic antidepressants (1 study, 38 participants; MD -19.78 points, 95% CI -20.25 to -19.31; very low-quality evidence), and flumazenil (3 studies, 58 participants; standardised mean difference -0.95, 95% CI -1.71 to -0.19; very low-quality evidence) at end of intervention. However, the positive effect of paroxetine on benzodiazepine withdrawal symptoms did not persist until longest follow-up (1 study, 54 participants; MD -0.13 points, 95% CI -4.03 to 3.77; very low-quality evidence).

The following pharmacological interventions reduced symptoms of anxiety at end of intervention: carbamazepine (1 study, 36 participants; MD -6.00 points, 95% CI -9.58 to -2.42; very low-quality evidence), pregabalin (1 study, 106 participants; MD -4.80 points, 95% CI -5.28 to -4.32; very low-quality evidence), captodiame (1 study, 81 participants; MD -5.70 points, 95% CI -6.05 to -5.35; very low-quality evidence), paroxetine (2 studies, 99 participants; MD -6.75 points, 95% CI -9.64 to -3.86; very low-quality evidence), and flumazenil (1 study, 18 participants; MD -1.30 points, 95% CI -2.28 to -0.32; very low-quality evidence).

Two pharmacological treatments seemed to reduce the proportion of participants that relapsed to benzodiazepine use: valproate (1 study, 27 participants; RR 0.31, 95% CI 0.11 to 0.90; very low-quality evidence) and cyamemazine (1 study, 124 participants; RR 0.33, 95% CI 0.14 to 0.78; very low-quality evidence). Alpidem decreased the proportion of participants with benzodiazepine discontinuation (1 study, 25 participants; RR 0.41, 95% CI 0.17 to 0.99; number needed to treat for an additional harmful outcome (NNTH) 2.3 participants; low-quality evidence) and increased the occurrence of withdrawal syndrome (1 study, 145 participants; RR 4.86, 95% CI 1.12 to 21.14; NNTH 5.9 participants; low-quality evidence). Likewise, magnesium aspartate decreased the proportion of participants discontinuing benzodiazepines (1 study, 144 participants; RR 0.80, 95% CI 0.66 to 0.96; NNTH 5.8; very low-quality evidence).

Generally, adverse events were insufficiently reported. Specifically, one of the flumazenil trials was discontinued due to severe panic reactions.

Authors' conclusions

Given the low or very low quality of the evidence for the reported outcomes, and the small number of trials identified with a limited number of participants for each comparison, it is not possible to draw firm conclusions regarding pharmacological interventions to facilitate benzodiazepine discontinuation in chronic benzodiazepine users. Due to poor reporting, adverse events could not be reliably assessed across trials. More randomised controlled trials are required with less risk of systematic errors ('bias') and of random errors ('play of chance') and better and full reporting of patient-centred and long-term clinical outcomes. Such trials ought to be conducted independently of industry involvement.

PLAIN LANGUAGE SUMMARY

Medications for discontinuation of long-term benzodiazepine use

Background

Benzodiazepines are widely prescribed for long-term use despite recommendations of only short-term use. It is often difficult to discontinue benzodiazepines after more than a few weeks of treatment due to the development of physical and psychological dependence. This review aimed to assess the effect and safety of medications to facilitate benzodiazepine discontinuation in chronic benzodiazepine users.

Search date

The evidence is current to October 2017.

Study characteristics

We identified 38 randomised controlled trials involving 2543 participants who had either been treated for more than two months with benzodiazepines, or who had been diagnosed with benzodiazepine dependence. We included studies irrespective of whether benzodiazepines were prescribed for anxiety, insomnia, or any other condition.

The average age of participants was around 50 years, and the majority of participants were women in most studies. Twenty-four trials were conducted in Europe; eight trials in the US or Canada; and six trials in Asia. The trials involved a wide range of medications to facilitate reduction or discontinuation of benzodiazepine use. Fourteen of the 38 included studies were partly funded by the drug manufacturer; nine studies were funded by government agencies; and 15 studies did not state the source of funding. The duration of the trials ranged between 1 and 24 weeks; the average trial duration was 9 weeks.

Key results

We extracted data on 18 different comparisons in a total of 2295 participants. We are uncertain whether valproate and tricyclic antidepressants increase the chance of discontinuing benzodiazepines, and whether benzodiazepine withdrawal symptoms are reduced by pregabalin, captodiame, paroxetine, tricyclic antidepressants, and flumazenil, as we assessed the quality of the evidence as very low. We are uncertain as to whether symptoms of anxiety after withdrawal of benzodiazepines are reduced by carbamazepine, pregabalin, captodiame, paroxetine, and flumazenil, as we assessed the quality of the evidence as very low. The effects of the evaluated medications were too uncertain to inform clinical practice due to risk of bias (systematic errors with overestimation of benefits and underestimation of harms) and risk of chance occurrence (random errors giving any result). Tolerability and safety were poorly reported across the included studies, making it impossible to assess the balance between possible benefits and adverse effects. Consequently, no conclusions can be drawn about the effectiveness of the interventions.

Quality of the evidence

The quality of the evidence was generally low or very low due to the small number of trials including a limited number of participants for each comparison; dissimilar results across studies; poor study design; and pronounced financial involvement of the pharmaceutical industry. Randomised controlled trials are therefore needed without risk of bias and random significant results involving long-term assessments of participants conducted without involvement of industry.

Summary of findings for the main comparison. Valproate compared with placebo or no intervention for benzodiazepine discontinuation in chronic benzodiazepine users

Valproate compared with placebo or no intervention for benzodiazepine discontinuation in chronic benzodiazepine users

Patient or population: adults who withdraw from chronic benzodiazepine use
Settings: outpatients
Intervention: valproate
Comparison: placebo or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo or no intervention	Valproate				
Benzodiazepine discontinuation, end of intervention	**Study population**		**RR 2.55** (1.08 to 6.03)	27 (1 study)	⊕⊖⊖⊖ **very low**[1,2]	The required information size of 1918 participants was not met.
	679 per 1000	**1000 per 1000** (142 to 1000)				
Benzodiazepine discontinuation, longest follow-up	**Study population**		**RR 1.57** (0.80 to 3.09)	24 (1 study)	⊕⊖⊖⊖ **very low**[1,2]	
	500 per 1000	**785 per 1000** (400 to 1000)				
Benzodiazepine withdrawal symptoms, end of intervention		The mean benzodiazepine withdrawal symptoms in the intervention groups was **0.15 standard deviations lower** (0.68 lower to 0.37 higher).		56 (2 studies)	⊕⊖⊖⊖ **very low**[3,4]	SMD -0.15 (-0.68 to 0.37). As a rule of thumb, 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect.
Benzodiazepine withdrawal symptoms, longest follow-up	Not estimable		-	(0 study)		No included study measured this outcome.

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

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

[1]No details provided regarding random sequence generation, allocation concealment, and blinding, leading to unclear risk of selection bias, performance and detection bias (downgraded one level).
[2]Required information size not met (downgraded two levels due to serious imprecision: the sample size is far from the required one).
[3]Unclear risk of selection bias, attrition bias, reporting bias and high risk of performance bias (downgraded one level).
[4]Required information size not met (downgraded two levels due to serious imprecision).

Summary of findings 2. Carbamazepine compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users

Carbamazepine compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users

Patient or population: adults who withdraw from chronic benzodiazepine use
Settings: outpatients
Intervention: carbamazepine
Comparison: 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				
	Placebo	Carbamazepine				
Benzodiazepine discontinuation, end of intervention	**Study population**		**RR 1.33** (0.99 to 1.8)	147 (3 studies)	⊕⊕⊖⊖ **low**[1,2]	Trial Sequential Analysis showed that only 7.0% of the required information size (2109) was reached, indicating that insufficient information has been obtained.
	480 per 1000	**638 per 1000** (475 to 864)				
Benzodiazepine discontinuation, longest follow-up	**Study population**		**RR 1.41** (0.86 to 2.29)	40 (1 study)	⊕⊖⊖⊖ **very low**[3,4]	
	524 per 1000	**739 per 1000** (450 to 1000)				
Benzodiazepine withdrawal symptoms, end of intervention		The mean benzodiazepine withdrawal symptoms in the intervention groups was		76 (2 studies)	⊕⊖⊖⊖ **very low**[1,5,6]	SMD -1.14 (-2.43 to 0.16).

		1.14 standard deviations lower (2.43 lower to 0.16 higher).			As a rule of thumb, 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect.
Benzodiazepine withdrawal symptoms, longest follow-up	Not estimable		-	(0 study)	No included study measured this outcome.

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

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

[1]Unclear risk of selection bias. One study with high risk of attrition, reporting, and other bias (downgraded one level).
[2]Required information size not met (downgraded one level due to imprecision).
[3]Unclear risk of selection and attrition bias (downgraded one level).
[4]Required information size not met, and 95% CI includes both no effect and appreciable benefit (downgraded two levels due to imprecision).
[5]Required information size not met (downgraded one level for imprecision).
[6]Significant heterogeneity (downgraded one level for inconsistency).

Summary of findings 3. Lithium compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users

Lithium compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users

Patient or population: adults who withdraw from chronic benzodiazepine use
Settings: outpatients
Intervention: lithium
Comparison: 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**				
	Placebo	**Lithium**				

Benzodiazepine discontinuation, end of intervention	**Study population**		**RR 1.05** (0.86 to 1.28)	230 (1 study)	⊕⊕⊖⊖ **low**[1,2]	The required information size of 1918 participants was not met.
	617 per 1000	**648 per 1000** (531 to 790)				
Benzodiazepine discontinuation, longest follow-up	Not estimable	-	-	(0 study)	-	No included studies measured this outcome.
Benzodiazepine withdrawal symptoms, end of intervention	Not estimable	-	-	(0 study)	-	No included studies measured this outcome.
Benzodiazepine withdrawal symptoms, longest follow-up	Not estimable	-	-	(0 study)	-	No included study measured this outcome.

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

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

[1]Unclear risk of selection, attrition, and reporting bias (downgraded one level).
[2]The required information size of 1918 participants was not met (downgraded one level due to imprecision).

Summary of findings 4. Pregabalin compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users

Pregabalin compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users

Patient or population: adults who withdraw from chronic benzodiazepine use
Settings: outpatients
Intervention: pregabalin
Comparison: 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**				
	Placebo	**Pregabalin**				

Benzodiazepine discontinuation, end of intervention	**Study population**		**RR 1.44** (0.92 to 2.25)	106 (1 study)	⊕⊖⊖⊖ **very low**[1,2]	The required information size of 1918 participants was not met.
	360 per 1000	**518 per 1000** (331 to 810)				
Benzodiazepine discontinuation, longest follow-up	Not estimable	-	-	(0 study)	-	No included studies measured this outcome.
Benzodiazepine withdrawal symptoms, Physician Withdrawal Checklist (PWCL), end of intervention	-	The mean benzodiazepine withdrawal symptoms, PWCL, end of intervention in the intervention group was **3.10 lower** (3.51 to 2.69 lower).	-	106 (1 study)	⊕⊖⊖⊖ **very low**[1,2]	MD -3.10 (-3.51 to -2.69)
Benzodiazepine withdrawal symptoms, longest follow-up	Not estimable	-	-	(0 study)	-	No included study measured this outcome.

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

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

[1]Unclear risk of selection bias and high risk of attrition and other bias (downgraded two levels).
[2]Required information size not met (downgraded one level due to imprecision).

Summary of findings 5. Captodiame compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users

Captodiame compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users

Patient or population: adults who withdraw from chronic benzodiazepine use
Settings: outpatients
Intervention: captodiame
Comparison: 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				
	Placebo	Captodiame				
Benzodiazepine discontinuation, end of intervention	Not estimable	-	-	(0 study)	-	No included studies measured this outcome.
Benzodiazepine discontinuation, longest follow-up	Not estimable	-	-	(0 study)	-	No included studies measured this outcome.
Benzodiazepine withdrawal symptoms, Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ), end of intervention	-	The mean benzodiazepine withdrawal symptoms, BWSQ, end of intervention in the intervention group was **1.00 lower** (1.13 to 0.87 lower).	-	81 (1 study)	⊕⊖⊖⊖ **very low**[1,2]	MD -1.00 (-1.13 to -0.87) The required information size of 229 participants was not met.
Benzodiazepine withdrawal symptoms, longest follow-up	Not estimable	-	-	(0 study)	-	No included study measured this outcome.

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

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

[1]Unclear risk of selection and reporting bias. High risk of other bias (downgraded one level).
[2]Required information size not met (downgraded two levels due to imprecision).

Summary of findings 6. Paroxetine compared with placebo or no intervention for benzodiazepine discontinuation in chronic benzodiazepine users

Paroxetine compared with placebo or no intervention for benzodiazepine discontinuation in chronic benzodiazepine users

Patient or population: adults who withdraw from chronic benzodiazepine use
Settings: outpatients

Intervention: paroxetine
Comparison: placebo or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo or Control	Paroxetine				
Benzodiazepine discontinuation, end of intervention	**Study population**		**RR 1.45** (0.88 to 2.39)	221 (3 studies)	⊕⊖⊖⊖ **very low**[1,2]	Trial Sequential Analysis showed that only 2.34% of the required information size (9448) was reached, indicating that insufficient information has been obtained.
	504 per 1000	**731 per 1000** (444 to 1000)				
Benzodiazepine discontinuation, longest follow-up	Not estimable		-	(0 study)	-	No included study measured this outcome.
Benzodiazepine withdrawal symptoms, BWSQ, end of intervention	-	The mean benzodiazepine withdrawal symptoms, BWSQ, end of intervention in the intervention groups was **3.57 lower** (5.34 to 1.8 lower).	-	99 (2 studies)	⊕⊖⊖⊖ **very low**[3,4]	MD -3.57 (-5.34 to -1.8). Trial Sequential Analysis showed that the required information size of 229 participants was not reached. However, the alpha-spending boundaries for benefit were crossed, indicating that sufficient information was obtained, and the result was not due to random error.
Benzodiazepine withdrawal symptoms, BWSQ, longest follow-up: 6 months	-	The mean benzodiazepine withdrawal symptoms, BWSQ, longest follow-up: 6 months in the intervention group was **0.13 lower** (4.03 lower to 3.77 higher).	-	54 (1 study)	⊕⊖⊖⊖ **very low**[5,6]	MD -0.13 (-4.03 to 3.77)

*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).
BWSQ: Benzodiazepine Withdrawal Symptom Questionnaire; **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

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

Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Unclear risk of selection and attrition bias. High risk of performance, detection, reporting, and other bias (downgraded two levels).
[2]Required information size not met (downgraded one level due to imprecision).
[3]Unclear risk of selection bias. High risk of performance, detection, reporting, and other bias (downgraded two levels).
[4]The required information size was not met (downgraded one level due to imprecision).
[5]Unclear risk of selection bias. High risk of reporting and other bias (downgraded one level).
[6]Required information size not met (downgraded two levels due to imprecision).

Summary of findings 7. Tricyclic antidepressants compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users

Tricyclic antidepressants compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users

Patient or population: adults who withdraw from chronic benzodiazepine use
Settings: outpatients
Intervention: tricyclic antidepressants
Comparison: 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				
	Placebo	Tricyclic antidepressants				
Benzodiazepine discontinuation, end of intervention	**Study population**		**RR 0.82** (0.52 to 1.28)	105 (2 studies)	⊕⊖⊖⊖ **very low**[1,2]	Trial Sequential Analysis showed that only 7.82% of the required information size (1343) was reached, indicating that insufficient information has been obtained.
	451 per 1000	**370 per 1000** (235 to 577)				
Benzodiazepine discontinuation, longest follow-up	**Study population**		**RR 2.2** (1.27 to 3.82)	47 (1 study)	⊕⊕⊖⊖ **low**[3,4]	
	375 per 1000	**825 per 1000** (476 to 1000)				
Benzodiazepine withdrawal symptoms, Physician Withdrawal Checklist, end of intervention	-	The mean benzodiazepine withdrawal symptoms in the intervention group was 19.78**lower** (20.25 lower to 19.31 lower).	-	38 (1 study)	⊕⊖⊖⊖ **very low**[4,5]	MD -19.78 (-20.25 to -19.31)

Benzodiazepine withdrawal symptoms, longest follow-up	Not estimable	-	-	(0 study)	-	No included study measured this outcome.

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

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

[1]Unclear risk of selection bias and high risk of attrition and other bias (downgraded one level).
[2]Required information size not met (downgraded one level due to imprecision).
[3]Unclear risk of selection and attrition bias (downgraded one level).
[4]Required information size not met (downgraded two levels due to imprecision).
[5]High risk of performance, detection, and reporting bias (downgraded two levels).

Summary of findings 8. Alpidem compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users

Alpidem compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users

Patient or population: adults who withdraw from chronic benzodiazepine use
Settings: outpatients
Intervention: alpidem
Comparison: 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				
	Placebo	Alpidem				
Benzodiazepine discontinuation, end of intervention	**Study population**		**RR 0.41** (0.17 to 0.99)	25 (1 study)	⊕⊕⊝⊝ **low**[1]	The required information size of 1918 participants was not met.
	750 per 1000	**308 per 1000** (128 to 743)				

Benzodiazepine discontinuation, longest follow-up	Not estimable	-	-	(0 study)	-	No included study measured this outcome.
Withdrawal syndrome (clinical diagnosis), end of intervention	**Study population**		**RR 4.86** (1.12 to 21.14)	145 (1 study)	⊕⊖⊖⊖ **low**[2,3]	
	29 per 1000	**143 per 1000** (33 to 622)				
Benzodiazepine withdrawal symptoms, longest follow-up	Not estimable	-	-	(0 study)	-	No included study measured this outcome.

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

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

[1]Required information size not met (downgraded two levels due to imprecision).
[2]Required information size not met (downgraded one level due to imprecision).
[3]Unclear risk of selection and other bias, high risk of attrition bias (downgraded one level)

Summary of findings 9. Buspirone compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users

Buspirone compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users

Patient or population: adults who withdraw from chronic benzodiazepine use
Settings: outpatients
Intervention: buspirone
Comparison: 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**				
	Placebo	**Buspirone**				
	Study population		**RR 0.82** (0.49 to 1.37)	143 (4 studies)		

Benzodiazepine discontinuation, end of intervention	**563 per 1000**	**462 per 1000** (276 to 772)			⊕⊕⊖⊖ **low**[1,2]	Trial Sequential Analysis showed that only 4.23% of the required information size (3381) was reached, indicating that insufficient information has been obtained.
Benzodiazepine discontinuation, longest follow-up	**Study population**		**RR 0.60** (0.34 to 1.05)	23 (1 study)	⊕⊕⊖⊖ **low**[2,3]	
	917 per 1000	**550 per 1000** (312 to 962)				
Benzodiazepine withdrawal symptoms, end of intervention	-	The mean benzodiazepine withdrawal symptoms, end of intervention in the intervention groups was **4.69 higher** (14.47 lower to 23.85 higher).	-	17 (1 study)	⊕⊖⊖⊖ **very low**[1,4]	MD 4.69 (-14.47 to 23.87)
Benzodiazepine withdrawal symptoms, longest follow-up	-	The mean benzodiazepine withdrawal symptoms, longest follow-up in the intervention groups was **1.34 lower** (14.31 lower to 11.63 higher).	-	15 (1 study)	⊕⊖⊖⊖ **very low**[3,4]	MD -1.34 (-14.31 to 11.63)

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

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

[1]Unclear risk of selection, performance, and reporting bias. High risk of attrition and other bias (downgraded one level).
[2]Required information size not met (downgraded one level due to imprecision).
[3]Unclear risk of selection and reporting bias. High risk of attrition bias (downgraded one level).
[4]Reguired information size not met (downgraded two levels due to serious imprecision).

Summary of findings 10. Melatonin compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users

Melatonin compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users

Patient or population: adults who withdraw from chronic benzodiazepine use
Settings: outpatients (3 studies), outpatients in methadone maintenance treatment (1 study)
Intervention: melatonin
Comparison: 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				
	Placebo	Melatonin				
Benzodiazepine discontinuation, end of intervention	**Study population**		**RR 1.20** (0.73 to 1.96)	219 (4 studies)	⊕⊖⊖⊖ **very low**[1,2]	Trial Sequential Analysis showed that only 6.37% of the required information size (3438) was reached, indicating that insufficient information has been obtained.
	417 per 1000	**500 per 1000** (304 to 817)				
Benzodiazepine discontinuation, longest follow-up	**Study population**		**RR 1.03** (0.47 to 2.27)	38 (1 study)	⊕⊖⊖⊖ **very low**[2,3,4]	
	389 per 1000	**401 per 1000** (183 to 883)				
Benzodiazpine withdrawal symptoms, end of intervention	Not estimable	-	-	(0 study)	-	No included study measured this outcome.
Benzodiazepine withdrawal symptoms, longest follow-up	Not estimable	-	-	(0 study)	-	No included study measured this outcome.

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

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

Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Unclear risk of selection, attrition, and reporting bias. High risk of other bias (downgraded one level).
[2]Required information size not met, and the 95% CI includes both no effect and appreciable benefit (downgraded two levels due to imprecision).
[3]Unclear risk of selection and reporting bias (downgraded one level).
[4]Required information size not met (downgraded two levels due to imprecision).

Summary of findings 11. Flumazenil compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users

Flumazenil compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users

Patient or population: adults who withdraw from chronic benzodiazepine use
Settings: outpatients in methadone maintenance treatment (2 studies), outpatients (1 study)
Intervention: flumazenil
Comparison: 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				
	Placebo	Flumazenil				
Benzodiazepine discontinuation, end of intervention	Not estimable	-	-	(0 study)	-	No included study measured this outcome.
Benzodiazepine discontinuation, longest follow-up	Not estimable	-	-	(0 study)	-	No included study measured this outcome.
Benzodiazepine withdrawal symptoms, end of intervention	-	The mean benzodiazepine withdrawal symptoms, end of intervention in the intervention groups was **0.95 standard deviations lower** (1.71 to 0.19 lower).	-	58 (3 studies)	⊕⊝⊝⊝ **very low**[1,2]	SMD -0.95 (-1.71 to -0.19) As a rule of thumb, 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect.
Benzodiazepine withdrawal symptoms, longest follow-up	Not estimable	-	-	(0 study)	-	No included study measured this outcome.

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

CI: confidence interval; **SMD:** standardised mean difference

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

[1]Unclear risk of selection bias and high risk of performance, detection, and other bias (downgraded one level).
[2]Required information size not met (downgraded two levels due to imprecision).

Summary of findings 12. Progesterone compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users

Progesterone compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users

Patient or population: adults who withdraw from chronic benzodiazepine use
Settings: outpatients
Intervention: progesterone
Comparison: 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				
	Placebo	Progesterone				
Benzodiazepine discontinuation, end of intervention	**Study population**		**RR 1.15** (0.52 to 2.54)	35 (1 study)	⊕⊝⊝⊝ **very low**[1,2]	The required information size of 1918 participants was not met.
	417 per 1000	**479 per 1000** (217 to 1000)				
Benzodiazepine discontinuation, longest follow-up	Not estimable	-	-	(0 study)	-	No included study measured this outcome.
Benzodiazepine withdrawal symptoms, end of intervention	Not estimable	-	-	(0 study)	-	No included study measured this outcome.
Benzodiazepine withdrawal symptoms, longest follow-up	Not estimable	-	-	(0 study)	-	No included study measured this outcome.

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

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

[1]Unclear risk of selection and attrition bias (downgraded one level).
[2]Required information size not met, and the 95% CI includes both no effect and appreciable benefit (downgraded two levels due to imprecision).

Summary of findings 13. Magnesium aspartate compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users

Magnesium aspartate compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users

Patient or population: adults who withdraw from chronic benzodiazepine use
Settings: outpatients
Intervention: magnesium aspartate
Comparison: 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				
	Placebo	Magnesium aspartate				
Benzodiazepine discontinuation, end of intervention	**Study population**		**RR 0.80** (0.66 to 0.96)	144 (1 study)	⊕⊖⊖⊖ **very low**[1,2]	The required information size of 1918 participants was not met.
	853 per 1000	**683 per 1000** (563 to 819)				
Benzodiazepine discontinuation, longest follow-up	Not estimable	-	-	(0 study)	-	No included study measured this outcome.
Benzodiazepine withdrawal symptoms, end of intervention	Not estimable	-	-	(0 study)	-	No included study measured this outcome.

Benzodiazepine withdrawal symptoms, longest follow-up	Not estimable	-	-	(0 study)	-	No included study measured this outcome.

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

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

[1]Unclear risk of selection, detection, and attrition bias (downgraded one level).
[2]Required information size not met (downgraded two levels due to imprecision).

Summary of findings 14. Homéogène 46/Sedatif PC (homeopathic drugs) compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users

Homéogène 46/Sedatif PC (homeopathic drugs) compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users

Patient or population: adults who withdraw from chronic benzodiazepine use
Settings: outpatients
Intervention: Homéogène 46/Sedatif PC (homeopathic drugs)
Comparison: 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**				
	Placebo	**Homéogène 46/ Sedatif PC (homeopathic drugs)**				
Benzodiazepine discontinuation, end of intervention	**Study population**		**RR 0.79** (0.36 to 1.7)	51 (1 study)	⊕⊖⊖⊖ **very low**[1,2]	The required information size was not met.
	381 per 1000	**301 per 1000** (137 to 648)				

Benzodiazepine discontinuation, longest follow-up	Not estimable	-	-	(0 study)	-	No included study measured this outcome.
Benzodiazepine withdrawal symptoms, end of intervention	Not estimable	-	-	(0 study)	-	No included study measured this outcome.
Benzodiazepine withdrawal symptoms, longest follow-up	Not estimable	-	-	(0 study)	-	No included study measured this outcome.

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

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

[1]Unclear risk of selection, attrition, and other bias (downgraded one level).
[2]Required information size not met, and the 95% CI includes both no effect and appreciable benefit (downgraded two levels due to imprecision).

Summary of findings 15. Carbamazepine compared with tricyclic antidepressant for benzodiazepine discontinuation in chronic benzodiazepine users

Carbamazepine compared with tricyclic antidepressant for benzodiazepine discontinuation in chronic benzodiazepine users

Patient or population: adults who withdraw from chronic benzodiazepine use
Settings: outpatients
Intervention: carbamazepine
Comparison: tricyclic antidepressant

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Tricyclic antidepressant	Carbamazepine				

Benzodiazepine discontinuation, end of intervention	**Study population**		**RR 1.00** (0.78 to 1.29)	48 (1 study)	⊕⊕⊖⊖ **low**[1,2]	The required information size was not met.
	833 per 1000	**833 per 1000** (650 to 1000)				
Benzodiazepine discontinuation, longest follow-up	Not estimable	-	-	(0 study)	-	No included study measured this outcome.
Benzodiazepine withdrawal symptoms, end of intervention	Not estimable	-	-	(0 study)	-	No included study measured this outcome.
Benzodiazepine withdrawal symptoms, longest follow-up	Not estimable	-	-	(0 study)	-	No included study measured this outcome.

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

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

[1]Unclear risk of selection, detection, and attrition bias (downgraded one level).
[2]Required information size not met (downgraded one level due to imprecision).

BACKGROUND

Description of the condition

Benzodiazepines are widely prescribed, and consumption remains high despite a modest overall decline during the last couple of decades (Islam 2014; Tsimtsiou 2009). A US national survey indicated a prevalence of benzodiazepine consumption of 3.8% among non-institutionalised adults (Paulose-Ram 2007), and the prevalence approached 8% in a Dutch survey of elderly people (Sonnenberg 2012). Another US survey reported an increase in the percentage of adults filling a benzodiazepine prescription from 4.1% in 1996 to 5.6% in 2013 (Bachhuber 2016). A survey in a New Zealand psychiatric outpatient setting documented that one-third of the patients were prescribed benzodiazepines or benzodiazepine-like drugs, and the majority of prescriptions were long-standing (Huthwaite 2013).

Benzodiazepines are indicated for short-term treatment of anxiety and insomnia, but prescriptions are often prolonged due to the development of dependence and a lack of knowledge of non-pharmacological management of anxiety, insomnia, and similar symptoms (Ashton 2005; Huthwaite 2013; O'Brien 2005). Gradual dose reduction of benzodiazepines is recommended above abrupt discontinuation to minimise withdrawal symptoms, including the risk of withdrawal seizures (Dell'osso 2013). The importance of individual adjustment of withdrawal rate is emphasised in clinical practice guidelines. The individually adjusted withdrawal rate should include consideration of benzodiazepine type and dosage, original reason for prescribing, environmental stressors, and amount of available support (Ashton 2005). The duration of tapering is thus sometimes prolonged for months or years; however, very slow tapering rates do not seem superior to faster tapering regimens (Parr 2009). Withdrawal symptoms may manifest both physically (e.g. flu-like complaints, muscle cramps) and psychologically (e.g. irritability, insomnia, perceptual changes, anxiety, depersonalisation, derealisation) (Baldwin 2013). Withdrawal symptoms therefore often resemble the symptoms that led to the initial benzodiazepine prescription**,** erroneously leading patients and caregivers to assume that continued prescription is required. Discontinuation is thus complicated by a mixture of withdrawal symptoms and original symptoms that might reoccur in an exaggerated form (rebound symptoms). Psychological interventions (e.g. relaxation training, psycho-education) for managing rebound symptoms are superior to gradual dose reduction alone in patients in primary care settings (Parr 2009). Adverse reactions associated with benzodiazepine treatment include cognitive impairment (Barker 2004; Glass 2005), psychomotor impairments with increased risk of falls, Woolcott 2009, and accidents (Smink 2010), daytime sedation (Glass 2005), and increased risk of dementia (Billioti 2012; Gallacher 2012; Wu 2009). Although benzodiazepines initially improve sleep continuity parameters (e.g. sleep latency, total sleep time) (Buscemi 2007a), the drugs decrease the amount of deep sleep (Parrino 1996), thereby exerting a negative effect on the overall sleep architecture. Moreover, development of tolerance to the sedative effects implies that the original dose of the drug has progressively less effect, and higher doses are needed to obtain the desired effect (Vinkers 2012). Another concern associated with prolonged benzodiazepine use is the increased mortality reported in a number of observational studies (Bachhuber 2016; Kripke 1998; Kripke 2012; Mallon 2009; Weich 2014). However, this issue is controversial because of conflicting results (Gisev 2011; Hausken 2007; Jaussent 2013), and the lack of appropriate confounder control in many of the studies showing increased mortality (Kripke 1998; Kripke 2012; Mallon 2009).

The majority of benzodiazepine prescriptions occur in general practice, where the following characteristics are associated with increased risk of long-term use: psychiatric comorbidity, older age, being less educated, being lonely, and using more avoidant coping behaviour (Zandstra 2004). In the elderly, benzodiazepine prescribing rates are especially high, and in this population prescriptions are associated with female sex, low level of education, low income, chronic physical diseases, functional limitations, cognitive impairment, depression, anxiety, and insomnia (Sonnenberg 2012). In opioid users, the additional use of benzodiazepines is associated with increased risk of adverse reactions and overdose due to the depression of the central nervous system exerted by both types of drugs, in particular in combination with alcohol intake (Jones 2014). Use of opioids is increasing, especially in the US, both as analgesics for people with chronic pain and as illicit drug use (Manchikanti 2008; Manchikanti 2012). The management of benzodiazepine dependence in subpopulations with comorbid substance abuse including opioid use therefore warrants attention.

Description of the intervention

Currently, no drugs are recommended or approved for the management of benzodiazepine dependence or facilitation of withdrawal after long-term use. Theoretically, a drug can facilitate benzodiazepine discontinuation in several ways: by ameliorating physical withdrawal symptoms (e.g. propranolol to reduce tremor and tachycardia); by reducing psychological craving (i.e. administering non-benzodiazepine sedating drugs); or by treating underlying insomnia or anxiety symptoms (e.g. melatonin, buspirone, imipramine). Antiepileptics and antidepressants are among the drugs most often evaluated, but with conflicting results (Parr 2009; Voshaar 2006). Abrupt cessation of benzodiazepine treatment followed by administration of flumazenil (a benzodiazepine receptor antagonist) has also been investigated (Gerra 2002), but the feasibility of this approach is limited by the intravenous administration formulation and the need for continuous medical monitoring. An intervention to facilitate benzodiazepine discontinuation can be administered with the aim of 1) benzodiazepine cessation and thereafter discontinuation of the experimental drug, or 2) substituting the ongoing benzodiazepine treatment, that is replacing the benzodiazepine treatment with another temporary or chronic drug with a more favourable adverse reaction profile.

How the intervention might work

A Cochrane Review covering the literature until October 2004 investigated pharmacological interventions for management of benzodiazepine mono-dependence in outpatient settings (Denis 2006). The conclusion was that gradual taper was preferable to abrupt discontinuation, and that carbamazepine, but not other investigated compounds, might be an effective intervention for gradual benzodiazepine discontinuation. However, the evidence was not strong enough to guide clinical recommendation. A meta-analysis including both inpatient and outpatient settings reported that augmentation of guided discontinuation programmes with imipramine was more effective than guided discontinuation

alone (Voshaar 2006). Another systematic review of approaches to benzodiazepine discontinuation in general practice and outpatient settings published in 2009 did not support substitutive pharmacotherapies to assist benzodiazepine discontinuation (Parr 2009). Psychological interventions have been found to be superior to gradual dose reduction (Parr 2009; Voshaar 2006), and are the topic of another recently published Cochrane Review (Darker 2015).

The pharmacological interventions hitherto investigated have tried to address the pharmacology of benzodiazepines and have thereby theoretically tried to counteract the withdrawal symptoms or to treat re-emerging insomnia and anxiety. In this respect, carbamazepine has been one of the most promising drugs so far (Denis 2006), but other drugs are accessible such as melatonin to counteract insomnia developed as part of the withdrawal syndrome (Garfinkel 1999), or pregabalin to reduce symptoms of general anxiety emerging or worsening when benzodiazepines are withdrawn (Hadley 2012).

Why it is important to do this review

Long-term benzodiazepine use is generally inappropriate due to adverse reactions (e.g. impaired psychomotor and cognitive functioning) and the risks of development of dependence and addiction. Distressing adverse reactions often complicate withdrawal attempts, and therefore it is important to evaluate whether any pharmacological intervention may facilitate the withdrawal or discontinuation of benzodiazepines. This could potentially minimise both individual and societal costs associated with the often extensive and prolonged withdrawal regimens. Since the previous reviews were conducted (Denis 2006; Parr 2009; Voshaar 2006), new studies investigating how to facilitate benzodiazepine discontinuation have been published, and a new systematic review was therefore warranted.

OBJECTIVES

To assess the benefits and harms of pharmacological interventions to facilitate discontinuation of chronic benzodiazepine use.

METHODS

Criteria for considering studies for this review

Types of studies

We included relevant randomised controlled trials irrespective of publication type, publication date, publication language, and publication status. We did not include quasi-randomised clinical studies and observational studies. In making this decision we are well aware that we achieve more focus on potential benefits and less on potential harms, since rare adverse events that develop only after long-term exposure are underestimated in randomised controlled trials.

Types of participants

Adult (aged 18 years or older) chronic benzodiazepine users defined as daily use of benzodiazepines for a minimum duration of two months; or people diagnosed with benzodiazepine dependence by any diagnostic criteria (e.g. International Classification of Diseases (ICD)-10: F13.1 or F13.2). We also included participants with psychiatric or somatic comorbidities. Benzodiazepines in this review included the benzodiazepine-like compounds (sometimes referred to as Z-drugs, e.g. zolpidem and zopiclone).

Types of interventions

Experimental intervention

The experimental intervention could be any drug administered to facilitate benzodiazepine withdrawal or to switch from benzodiazepine treatment to another drug. We included interventions conducted in general practice, outpatient settings, and in hospitalised patients.

Control intervention

The control interventions included:

- treatment as usual, as defined by the trialists;
- placebo;
- any active pharmacological comparator.

Co-interventions

Co-interventions of any kind were allowed, as long as they were delivered equally in both intervention groups.

Types of outcome measures

We assessed all outcomes at two time points:

- end of intervention, as defined by the trialists. This was the primary outcome time point in the review;
- longest follow-up, as defined by the trialists.

Primary outcomes

1. Benzodiazepine discontinuation (defined as cessation) measured by examining the blood or urine concentration of the participant or by self reported use.
2. Benzodiazepine withdrawal symptoms as measured by relevant questionnaires.
3. Serious adverse events, defined as any adverse event that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect (ICH GCP).

Secondary outcomes

1. Benzodiazepine mean dose.
2. Insomnia as measured by any relevant questionnaire.
3. Anxiety as measured by any relevant questionnaire.
4. Comorbid substance abuse as measured by self reported use of other drugs or alcohol.
5. Non-serious adverse events, defined as any non-serious undesirable medical event experienced by participants during a clinical trial that does not necessarily have a causal relationship with the intervention (ICH GCP).
6. Relapse to benzodiazepine use (defined according to the trialists), assessed only at longest follow-up after end of intervention among the subgroup of participants who discontinued benzodiazepine use at end of intervention.
7. Discontinuation due to adverse events assessed only at the end of intervention.

Search methods for identification of studies

We aimed to identify all relevant randomised controlled trials regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

We searched the following electronic databases:

- Cochrane Drugs and Alcohol Group's Specialised Register of Trials (searched on 17 October 2017);
- The Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 9);
- PubMed (January 1966 to 17 October 2017);
- Embase (Embase.com) (January 1974 to 17 October 2017);
- CINAHL (Cumulative Index to Nursing and Allied Health Literature) (EbscoHOST) (1982 to 17 October 2017);
- Web of Knowledge, Web of Science (1990 to 17 October 2017).

We searched the databases using MeSH and free-text terms relating to substance use disorders. We combined the PubMed search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision) (Lefebvre 2011). Detailed search strategies were developed for each database used, accounting for differences in controlled vocabulary and syntax rules. For details see Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6.

We searched the following trials registries on 17 October 2017:

- ClinicalTrials.gov (clinicaltrials.gov);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp);
- the ISRCTN registry (www.isrctn.com).

Searching other resources

We searched for further relevant trials by screening reference lists of previous review papers and those of all articles selected for inclusion.

Where possible, we contacted the first author of each included study to seek information about further relevant published and unpublished trials.

Data collection and analysis

Selection of studies

Two review authors (LB and BE, or LB and JR) independently screened titles of all studies obtained by the search strategy. After excluding all obviously irrelevant articles, we screened the abstracts of all remaining publications. We obtained all potentially relevant studies in full text, and two review authors independently assessed these studies for inclusion in the review (LB and BE, or LB and JR). During this process, we linked multiple reports of the same trial.

Data extraction and management

Two review authors (LB and BE, or LB and JR) extracted data from the included studies using a standard extraction form. Any disagreements were resolved by consensus between raters (LB and BE, or LB and JR), and if not possible by judgement of authors JL and CG.

We extracted the following data.

- General information: publication status, title, authors' names, source, country, contact address, language of publication, year of publication, duplicate publication.
- Trial characteristics: design and setting.
- Interventions: type of pharmacological intervention, dose, duration, type of control intervention.
- Participants: inclusion and exclusion criteria, number of participants in intervention and control groups, participant demographics such as sex and age, baseline characteristics, and number of participants lost to follow-up.
- Outcomes: please see Types of outcome measures above.
- Risk of bias: please see Assessment of risk of bias in included studies below.

Assessment of risk of bias in included studies

We assessed the risk of bias for randomised controlled trials using the criteria recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The recommended approach for assessing risk of bias in studies included in a Cochrane Review is a two-part tool, addressing seven specific domains, namely sequence generation and allocation concealment (selection bias), blinding of participants and providers (performance bias), blinding of outcome assessor (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias including industry bias (Lundh 2017). The first part of the tool involves describing what was reported to have happened in the trial. The second part of the tool involves assigning a judgement relating to the risk of bias for that entry, in terms of low, high, or unclear risk. To make these judgements we used the criteria indicated by the *Cochrane Handbook* adapted to the addiction field. See Appendix 7 for details.

We addressed the domains of sequence generation and allocation concealment (avoidance of selection bias) in the tool by a single entry for each study.

Regarding blinding of participants, personnel, and outcome assessor (avoidance of performance bias and detection bias), we planned to consider these items separately for objective outcomes (e.g. urine drug screening) and subjective outcomes (e.g. severity of signs and symptoms of withdrawal, adverse events). However, since all available outcomes were self reported, the dichotomisation into objective and subjective outcomes was not relevant.

We considered incomplete outcome data (avoidance of attrition bias) for all outcomes.

Overall assessment of risk of bias

We classified a trial as at low risk of bias only if all of the bias components described in the above paragraphs were classified as at low risk of bias. If one or more of the bias domains were classified as at unclear or high risk of bias, we classified the trial as at high risk of bias. If we found no trials at low risk of bias or only a very few trials at low risk of bias, we planned to identify a group of trials

with lower risk of bias, defined as those having low risk of bias in the following domains: generation of allocation sequence, allocation concealment, and blinding of participants and treatment providers. However, since we classified only one trial as at low risk of bias, and thus the majority of the trials (k = 37; 97%) as at high risk of bias, it was not possible to apply this classification in the current review.

Measures of treatment effect

For dichotomous outcomes, we calculated a risk ratio (RR) with 95% confidence interval (CI), and in case of a significant result based on trials at low risk of bias, we reported the number needed to treat for an additional beneficial outcome (NNTB) or the number needed to treat for an additional harmful outcome (NNTH) as the inverse of the absolute risk difference.

For continuous data, we calculated the mean difference (MD) between groups. We did not calculate effect size measures (standardised mean difference (SMD)) for all outcomes because of the inherent limitations associated with this measure (Higgins 2011). However, if scales of very considerable similarity were used, we could presume there was a small difference in the different measurements, and we calculated the effect size and planned to transform the effect back to the units of one or more of the specific instruments. However, due to marked differences in among-participant variability, we did not find it relevant to re-express the SMD using one of the specific measurement instruments.

Unit of analysis issues

The trial participant was the unit of analysis.

1. Cluster trials

No cluster-randomised trials were included. If one or more cluster-randomised trials had been included, we would have calculated the 'design effect' as described in our protocol (Baandrup 2015).

2. Cross-over trials

We used data only from the first phase of cross-over trials.

3. Studies with multiple intervention groups

Where a trial involved more than two intervention groups, we included both when relevant, or included data from the most relevant comparison if it was not appropriate from a clinical point of view to combine the experimental intervention groups into a single group (Higgins 2011).

Dealing with missing data

We tried to contact the first authors of studies to supply any missing data with regard to the defined outcomes. However, many of the included studies were old and the reported author contact details were outdated. It was thus impossible to contact many of the authors, and even the authors of newer studies did not reply to our queries for missing data.

Dichotomous data

For dichotomous outcomes, we did not impute missing values and analysed data as a complete-case analysis.

Continuous data

If standard deviations (SDs) were not reported, we calculated them, if possible, using other data from the trial. If calculation of the SD was impossible, we imputed SDs from trials with similar characteristics if we considered this to be a valid approach.

Assessment of heterogeneity

We assessed statistical heterogeneity in the trials both by visual inspection of a forest plot and by using a standard Chi^2 value with a significance level of P = 0.10. We assessed heterogeneity by use of the I^2 statistic. We interpreted an I^2 estimate greater than or equal to 50% and a significant Chi^2 statistic as evidence of substantial heterogeneity (Higgins 2011). If this was the case, we explored the reasons for heterogeneity. If there was high inconsistency, and a clear reason was found, we planned to present data separately. We only performed a meta-analysis if a sufficient number of studies were identified and if combining these studies was feasible as judged by clinical and statistical characteristics.

Assessment of reporting biases

We planned to inspect funnel plot symmetry when at least 10 trials were included in the meta-analysis (Egger 1997; Macaskill 2001), bearing in mind that publication bias does not necessarily cause asymmetry, and that asymmetry may have other causes than publication bias. The inspection by funnel plot was not possible because none of the meta-analyses included at least 10 trials.

For each included study, we investigated whether a study protocol was available. We searched PubMed, other major reference databases, and the Internet for a study protocol if a web address was not specifically stated in the article. This search could reveal abstracts or presentations relating to the study, and a comparison of outcomes with published outcomes was then possible. For newer studies, we searched for information on predefined outcome measures in trial registries. We had planned to construct a matrix containing recorded outcomes in each study, which then could indicate which studies did not report outcomes reported by the majority of included studies. However, during the process of data extraction and quality assessment, it was very evident which trials were associated with reporting bias, since these trials did not report the most evident outcome, namely some measure of benzodiazepine consumption.

Data synthesis

We divided the analyses according to type of experimental drug and pooling of drugs where a class effect could be expected (i.e. pooling of data from trials investigating drugs with a similar pharmacological profile, if clinical and statistical heterogeneity allowed). We performed meta-analyses according to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using the software Review Manager 5 (RevMan 2014). We further conducted Trial Sequential Analysis using the software available from CTU 2011.

Meta-analysis

We performed meta-analyses using a random-effects model based on expectations of substantial heterogeneity among included trials (Deeks 2011; DeMets 1987; DerSimonian 1986). However, in case we found that one or two trials dominated the reported evidence (i.e. constituted more than 75% of the evidence), and there was

substantial heterogeneity, we planned to synthesise data when appropriate and to emphasise results from the fixed-effect model. However, due to the nature of the extracted data this scenario was not relevant.

Trial Sequential Analysis

We applied Trial Sequential Analysis, CTU 2011; Thorlund 2011b, because cumulative meta-analyses are at risk of producing random errors due to sparse data and repetitive testing of the accumulating data (Brok 2008; Brok 2009; Thorlund 2009; Thorlund 2010; Wetterslev 2008; Wetterslev 2009). To minimise random errors, we calculated the required information size (i.e. the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) (Thorlund 2011a; Wetterslev 2008; Wetterslev 2017). The required information size for a meta-analysis corresponds to the sample size for a single trial (Wetterslev 2017). The required information size takes into account: the event proportion in the control group; the assumption of a plausible risk ratio (RR) reduction, or the RR reduction observed in the included trials with low risk of bias; and the assumed heterogeneity, Turner 2014, or diversity of the meta-analysis (Wetterslev 2008; Wetterslev 2009; Wetterslev 2017).

Trial Sequential Analysis enables testing for significance each time a new trial is added to the meta-analysis (Thorlund 2011b; Wetterslev 2008; Wetterslev 2017). We added the trials according to the year of publication, and if more than one trial had been published in a year, we added trials alphabetically according to the last name of the first author. On the basis of the required information size and risk of type I and type II errors, we further constructed trial sequential monitoring boundaries. These boundaries determine the statistical inference one may draw from a meta-analysis that has not reached the required information size. If the trial sequential boundary is crossed before the required information size is reached, firm evidence may perhaps be established and further trials may turn out to be superfluous. On the other hand, it is probably necessary to continue doing trials in order to detect or reject a certain intervention effect, if the trial sequential boundaries are not crossed.

As default, we originally planned to use a type I error of 5%, and a type II error of 20%. However, to account for multiplicity, we decreased the risk of type I error for the three primary outcomes to 2.5%, and to 1.25% for the seven secondary outcomes (Jakobsen 2014). Furthermore, we decreased the risk of type II error to 10%. For dichotomous outcomes, we had planned to estimate the required information size based on the proportion of participants with an outcome in the control group, a risk ratio of 20% or as suggested by the trials with low risk of bias, a diversity of 30% and 60%, or as suggested by the trials in the meta-analysis. Specifically, for the primary dichotomised outcome 'benzodiazepine discontinuation', we used a control event proportion of 48% for all analyses, as this was the observed mean for trials assessing this outcome. For continuous outcomes, we estimated the required information size based on the SD observed in the control group of trials with low risk of bias and a minimal relevant difference of 50% of this SD, a diversity of 30% and 60%, or as suggested by the trials in the meta-analysis. Specifically, for the secondary continuous outcome 'anxiety', assessed with the Hamilton Anxiety Rating Scale (HAM-A), we used a variance of 103 (corresponding to an SD of 10 points), and a minimal relevant difference of 5 points for all analyses, as this was the highest observed variance in the trials assessing this outcome. Likewise, we used a variance of 20 points (corresponding to an SD of 4.5 points), and a minimal relevant difference of 2.25 points for all analyses of benzodiazepine withdrawal symptoms assessed with the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ), as this was the highest observed variance in the trials assessing this outcome.

It was only possible to conduct Trial Sequential Analysis for eight outcomes, because fewer than two trials reported the same outcome, using the same instrument. In such situations the accrued information is such a small proportion of the required information size that Trial Sequential Analysis figures become uninterpretable.

Subgroup analysis and investigation of heterogeneity

We had planned to group the results from included studies according to the following methodological or clinical issues.

1. Trials at low risk of bias compared to trials at high risk of bias, or if we found no trials with low risk of bias, we would compare trials at lower risk of bias to trials at high risk of bias.
2. Type of benzodiazepine or benzodiazepine-related drug.
3. Trials with different types of treatment setting (e.g. general practice compared to outpatient setting compared to inpatient setting).
4. Trials with different modes of benzodiazepine tapering (e.g. prescheduled or symptom-guided).
5. Participants with concurrent psychiatric illness compared to participants without concurrent psychiatric illness.
6. Trials with different duration of the intervention: short (0 to 2 months), medium (3 to 6 months), and long (> 6 months).
7. Trials including inpatients compared to trials including outpatients.
8. Participants with other substance dependence versus participants with only benzodiazepine dependence/chronic use.

However, due to the high number of different pharmacological add-on agents with few trials per agent, we chose not to perform any of our planned subgroup analyses.

Sensitivity analysis

We had planned to perform a sensitivity analysis to examine the impact of our assumptions regarding missing data. Furthermore, we had planned a sensitivity analysis to investigate the influence of trials with low compliance with study medication compared to trials with high compliance with study medication (compliance as defined by the trialists).

Assumption for lost dichotomous data

We had planned to perform two sensitivity analyses:

- 'Best-worst-case' scenario: It will be assumed that all participants lost to follow-up in the experimental group had no outcome, and that all participants lost to follow-up in the control group had the outcome.
- 'Worst-best-case' scenario: It will be assumed that all participants lost to follow-up in the experimental group had the

outcome, and that all participants lost to follow-up in the control group had no outcome.

Assumptions for lost continuous data

Where assumptions had to be made regarding missing SDs (see: Dealing with missing data), we had planned sensitivity analysis to test how prone results were to change when 'completer' data only were compared to the imputed data using the above assumption. If there was a substantial difference, we had planned to report results and discuss them but continue to employ our assumption. Imputation of data turned out to be relevant for only one comparison: alpidem versus placebo (anxiety; Analysis 8.3).

However, due to the high number of different pharmacological add-on agents with few trials per agent, we chose not to perform any of our planned sensitivity analyses.

'Summary of findings'

We used the GRADE system to assess the quality of the body of evidence and constructed 'Summary of findings' tables for the two primary outcomes on benzodiazepine consumption, employing GRADEpro software (GRADE). We assessed five factors of the study design and implementation of available trials that may downgrade the quality of the evidence, namely: risk of bias; indirectness of evidence (population, intervention, control, outcomes); unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses); imprecision of results; and high probability of publication bias.

Based on this, we defined the levels of evidence as follows (Balshem 2011).

- High-quality evidence when "we are very confident that the true effect lies close to that of the estimate of the effect".
- Moderate-quality evidence when "we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different".
- Low-quality evidence when the following statement applies: "Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect".
- Very low-quality evidence when the following statement applies: "We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect".

RESULTS

Description of studies

See Characteristics of included studies section.

Results of the search

Our search strategy identified 3280 unique records. After removal of duplicates and irrelevant records, the number was reduced to 1239. Of these, we excluded 1174 after screening, and a further 22 after reviewing the full texts (Figure 1).

Figure 1. Study flow diagram.

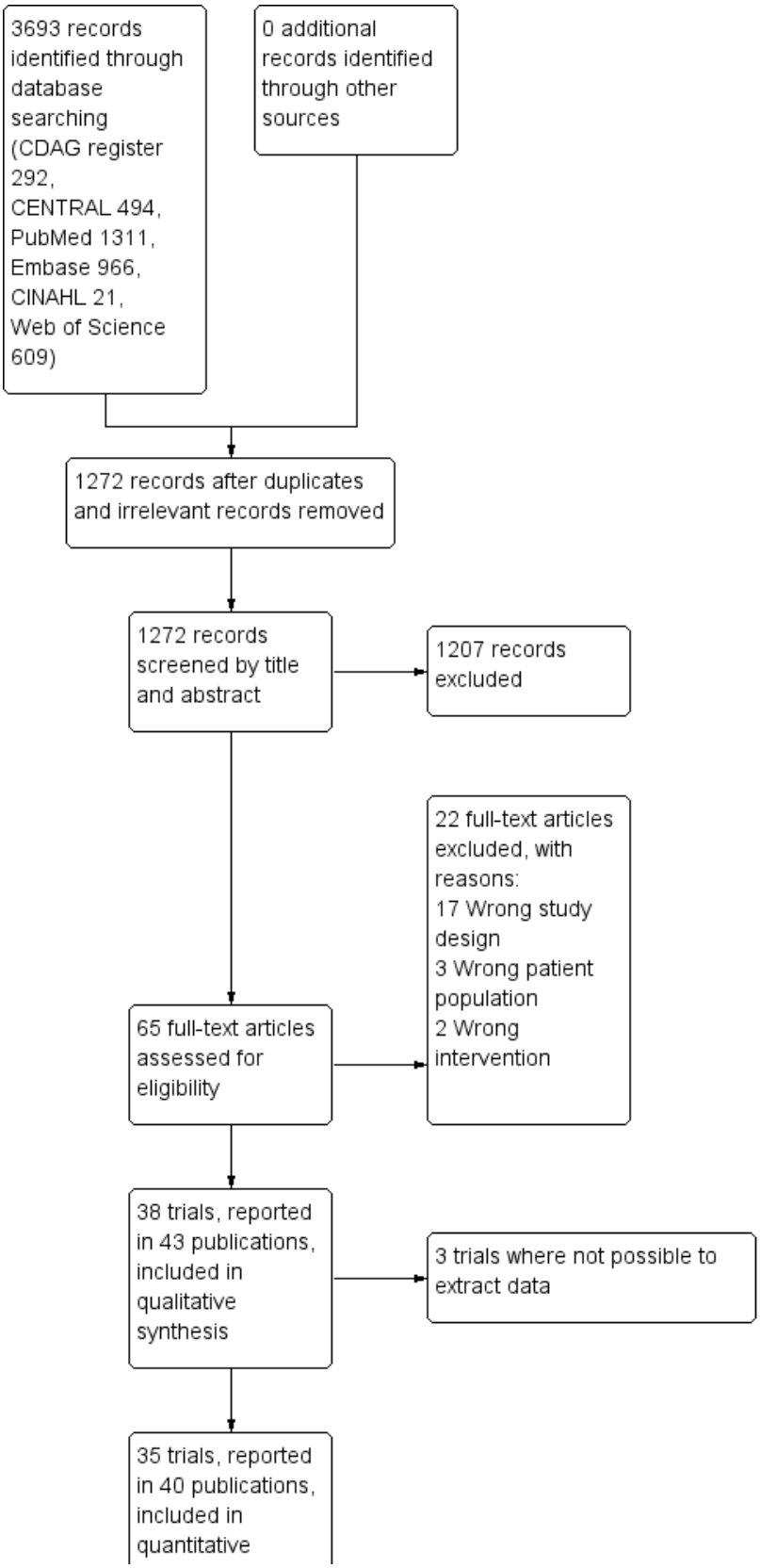
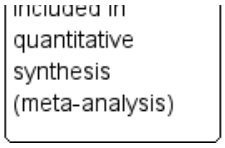


Figure 1. (Continued)



Included studies

We included 43 publications reporting on 38 trials. Due to general poor reporting of the trials, we were not able to extract relevant data from all of the trials, even after attempting to contact the authors where possible. For this reason, we have not extracted data from Romach 1998 (experimental drug: ondansetron), Saul 1989 (experimental drug: atenolol), and Mariani 2016 (experimental drug: gabapentin). As a result, we included 35 trials involving 2295 participants with data in the quantitative meta-analyses. See Characteristics of included studies.

Most of the trials (n = 35) involved a comparison between an active medication versus placebo or no intervention, while three trials investigated the experimental drug against another active comparator. The experimental drugs investigated were diverse, which limited the pooled analyses that were possible. If clinically relevant, we grouped investigational drugs with a similar mechanism, for example tricyclic antidepressants. To retain the clinical relevance of the meta-analyses, we did not group medications with dissimilar pharmacological action even though they may belong to the same Anatomical Therapeutic Chemical-group, for example valproate and carbamazepine trials were not pooled. The interventions investigated and included in the quantitative meta-analyses were as follows.

- Valproate versus placebo, Rickels 1999, or no intervention (Vorma 2011).
- Carbamazepine versus placebo (Di Costanzo 1992; Klein 1994; Schweizer 1991).
- Lithium versus placebo (Lecrubier 2005).
- Pregabalin versus placebo (Hadley 2012).
- Captodiame versus placebo (Mercier-Guyon 2004).
- Paroxetine versus placebo, GlaxoSmithKline 2002; Zitman 2001, or no intervention (Nakao 2006).
- Tricyclic antidepressants (dosulepin (Tyrer 1996), imipramine (Rickels 2000; Rynn 2003), or trazodone (Zhang 2013)) versus placebo.
- Alpidem versus placebo (Cassano 1996; Lader 1993).
- Buspirone versus placebo (Ashton 1990; Lader 1987; Morton 1995; Udelman 1990).
- Melatonin (short-acting, Peles 2007; Vissers 2007, and prolonged-release, Baandrup 2016; Garfinkel 1999) versus placebo.
- Flumazenil versus placebo (Gerra 1993; Gerra 2002; Harrison-Read 1996).
- Propranolol versus placebo (Tyrer 1981).
- Progesterone versus placebo (Schweizer 1995).
- Magnesium aspartate versus placebo (Hantouche 1998).
- Homeopathic drugs versus placebo (Cialdella 2001).
- Carbamazepine versus tricyclic antidepressant (tianeptine) (Kornowski 2002).
- Bromazepam versus cyamemazine (Lemoine 2006).
- Zopiclone versus flunitrazepam (Pat-Horenczyk 1998).

Out of the 38 trials, 24 were single-centre (Ashton 1990; Baandrup 2016; Cialdella 2001; Di Costanzo 1992; Garfinkel 1999; Gerra 1993; Gerra 2002; Harrison-Read 1996; Klein 1994; Kornowski 2002; Mariani 2016; Morton 1995; Nakao 2006; Pat-Horenczyk 1998; Peles 2007; Rickels 1999; Rickels 2000; Romach 1998; Rynn 2003; Schweizer 1991; Schweizer 1995; Tyrer 1996; Vorma 2011; Zhang 2013), and 14 were multicentre (Cassano 1996; GlaxoSmithKline 2002; Hadley 2012; Hantouche 1998; Lader 1987; Lader 1993; Lecrubier 2005; Lemoine 2006; Mercier-Guyon 2004; Saul 1989; Tyrer 1981; Udelman 1990; Vissers 2007; Zitman 2001).

The majority of the trials were performed in outpatient settings. The three trials investigating intravenous injection of flumazenil were conducted in inpatient settings (Gerra 1993; Gerra 2002; Harrison-Read 1996), as was a trial with rapid benzodiazepine dose reduction in opioid maintenance patients (Vorma 2011). In Gerra 1993 and Gerra 2002, participants were hospitalised for the duration of the trial (seven and eight days, respectively) whereas participants in Harrison-Read 1996 were hospitalised as they received a challenge with flumazenil and were thereafter treated as outpatients. Twenty-four trials were conducted in Europe; eight trials in the US or Canada; and six trials in Asia.

Nine trials reported the source of funding as research grants (Baandrup 2016; Cialdella 2001; Mariani 2016; Peles 2007; Rickels 1999; Rickels 2000; Schweizer 1991; Schweizer 1995; Vorma 2011), and the funding was unclear for 15 trials (Cassano 1996; Di Costanzo 1992; Gerra 1993; Gerra 2002; Hantouche 1998; Kornowski 2002; Lader 1987; Lader 1993; Lecrubier 2005; Nakao 2006; Saul 1989; Tyrer 1981; Tyrer 1996; Vissers 2007; Zhang 2013). Fourteen trials used medications provided by the manufacturing company (Ashton 1990; Garfinkel 1999; GlaxoSmithKline 2002; Hantouche 1998; Harrison-Read 1996; Klein 1994; Lemoine 2006; Mercier-Guyon 2004; Morton 1995; Pat-Horenczyk 1998; Romach 1998; Rynn 2003; Udelman 1990; Zitman 2001), and in all but one of these studies information regarding the degree of involvement of the pharmaceutical company was insufficient.

The trials investigated participants with a varying clinical picture dominated by anxiety. Three trials specifically investigated participants in opioid maintenance treatment (Mariani 2016; Peles 2007; Vorma 2011). In most trials, the majority of participants were women. The mean age was around 50 years (+/- 10 years) in most trials, and mean duration of benzodiazepine use was between 5 and 10 years in most trials. In eight trials there was no information at all on baseline characteristics. Eight trials applied abrupt discontinuation of benzodiazepine treatment with follow-up periods between 1 and 8 weeks, whereas the remainder of the trials applied a gradual benzodiazepine dosage reduction regimen lasting between 2 and 24 weeks.

Trial duration ranged between 1 and 24 weeks, and mean trial duration was 9.4 weeks.

Excluded studies

We excluded 22 studies that were considered potentially relevant and assessed in detail (Figure 1). The reasons for exclusion were: 17 studies had a study design not fulfilling our inclusion criteria; 3 studies had a patient population not fulfilling our inclusion criteria; and 2 studies had interventions not fulfilling our inclusion criteria. For further details see Characteristics of excluded studies section.

Risk of bias in included studies

The overall risk of bias associated with the included studies is summarised in Figure 2 and Figure 3. Please also see Characteristics of included studies table.

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

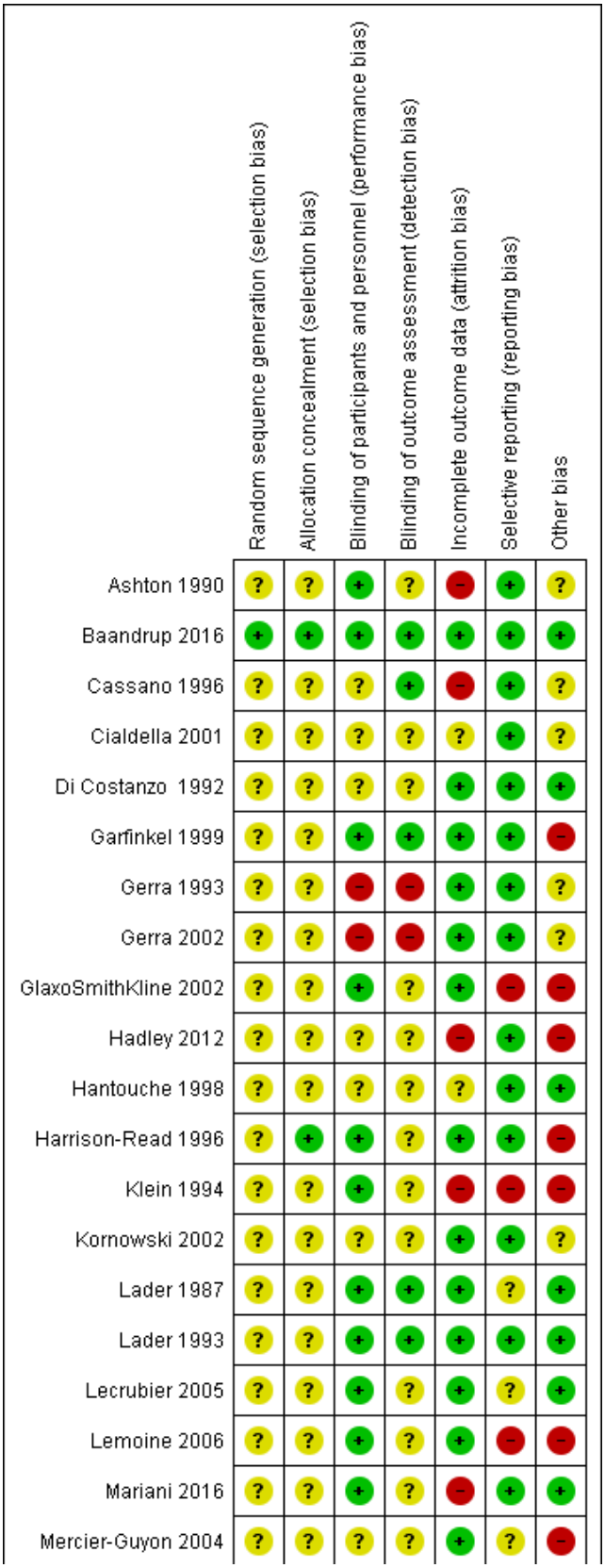


Figure 2. (Continued)

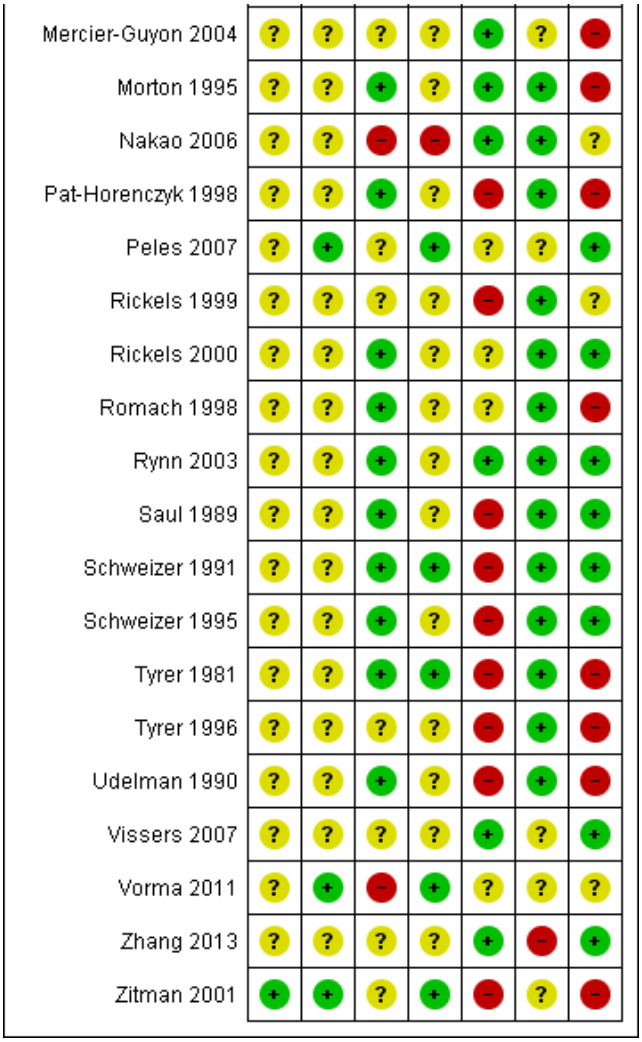
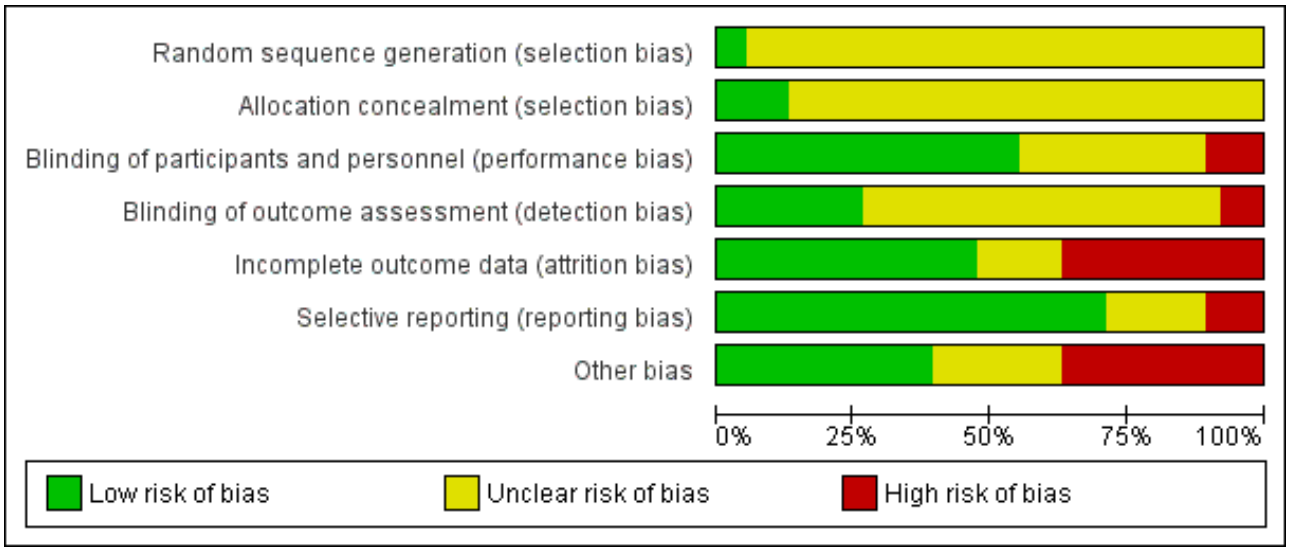


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Sequence generation

We judged only two trials as at low risk of bias because the random sequence was described as computer-generated (Baandrup 2016; Zitman 2001). For all other trials (n = 36; 95%), information on random sequence generation was not provided and they were therefore judged as at unclear risk of selection bias.

Allocation concealment

We judged five trials as at low risk of bias because they sufficiently described how the randomisation was administered in a way that staff and trial participants could not anticipate to which group the next participant would be randomised. In two trials, randomisation was administered by a third party who paced and distributed the trial medication using numbered medication containers (Baandrup 2016; Zitman 2001); in one trial consecutive container numbers were used (Peles 2007); in one trial allocation was performed by an independent pharmacist (Harrison-Read 1996); and one trial used sealed envelopes (Vorma 2011). We judged all other studies (n = 33; 87%) as at unclear risk of selection bias due to lack of information on allocation concealment.

Blinding

Performance bias

We evaluated 13 trials as at unclear risk of performance bias due to insufficient description of blinding procedures for participants and personnel (Cassano 1996; Cialdella 2001; Di Costanzo 1992; Hadley 2012; Hantouche 1998; Kornowski 2002; Mercier-Guyon 2004; Peles 2007; Rickels 1999; Tyrer 1996; Vissers 2007; Zhang 2013; Zitman 2001). We considered more than half of the trials (n = 21; 55%) as at low risk of performance bias due to sufficient blinding procedures of participants and personnel. Four of the included trials were not blinded for participants and personnel and were therefore judged as at high risk of performance bias (Gerra 1993; Gerra 2002; Nakao 2006; Vorma 2011).

Detection bias

The majority of included trials (n = 25; 66%) were associated with unclear risk of detection bias due to insufficient descriptions of what was done to ensure blinding of outcome assessors. Three of the included trials were not blinded for outcome assessors and were therefore judged as at high risk of detection bias (Gerra 1993; Gerra 2002; Nakao 2006). We judged 10 trials as at low risk of detection bias because they provided sufficient information on blinding of outcome assessors (Baandrup 2016; Cassano 1996; Garfinkel 1999; Lader 1987; Lader 1993; Peles 2007; Schweizer 1991; Tyrer 1981; Vorma 2011; Zitman 2001).

Incomplete outcome data

We judged 14 studies (37%) as at high risk of attrition bias due to unacceptably high dropout rates, that is close to 50% (Ashton 1990; Cassano 1996; Hadley 2012; Klein 1994; Lader 1987; Mariani 2016; Pat-Horenczyk 1998; Saul 1989; Schweizer 1991; Schweizer 1995; Tyrer 1981; Tyrer 1996; Udelman 1990; Zitman 2001). We judged six studies (16%) as at unclear risk of attrition bias due to missing information on flow of participants through the trials (Cialdella 2001; Hantouche 1998; Peles 2007; Rickels 2000; Romach 1998; Vorma 2011). We judged the remaining studies (n = 18; 47%) as at low risk of attrition bias.

Selective reporting

We judged four studies (11%) as at high risk of reporting bias because important outcome measures were not reported, that is benzodiazepine dosage at follow-up (GlaxoSmithKline 2002; Klein 1994; Zhang 2013), or reporting of an unusual primary outcome (Lemoine 2006). We judged seven studies (18%) as at unclear risk of reporting bias due to insufficient information regarding whether selective reporting was present (Lader 1987; Lecrubier 2005; Mercier-Guyon 2004; Peles 2007; Vissers 2007; Vorma 2011; Zitman 2001). We judged the remaining studies (n = 27; 71%) as at low risk of reporting bias.

Other potential sources of bias

We judged nine trials (24%) as at unclear risk of other bias mostly due to unclear or lacking description of funding. We rated 14 (37%) of the included trials as at high risk of other bias due to missing information on how the funding pharmaceutical company was involved in designing the trial as well as in analysing and interpreting the results.

Overall risk of bias

According to criteria described above, we could classify only one trial as at low risk of bias (Baandrup 2016), and no other trial qualified as at lower risk of bias. The large majority of the trials were thus at high risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Valproate compared with placebo or no intervention for benzodiazepine discontinuation in chronic benzodiazepine users; **Summary of findings 2** Carbamazepine compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users; **Summary of findings 3** Lithium compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users; **Summary of findings 4** Pregabalin compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users; **Summary of findings 5** Captodiame compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users; **Summary of findings 6** Paroxetine compared with placebo or no intervention for benzodiazepine discontinuation in chronic benzodiazepine users; **Summary of findings 7** Tricyclic antidepressants compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users; **Summary of findings 8** Alpidem compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users; **Summary of findings 9** Buspirone compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users; **Summary of findings 10** Melatonin compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users; **Summary of findings 11** Flumazenil compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users; **Summary of findings 12** Progesterone compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users; **Summary of findings 13** Magnesium aspartate compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users; **Summary of findings 14** Homéogène

46/Sedatif PC (homeopathic drugs) compared with placebo for benzodiazepine discontinuation in chronic benzodiazepine users; **Summary of findings 15** Carbamazepine compared with tricyclic antidepressant for benzodiazepine discontinuation in chronic benzodiazepine users

Valproate versus placebo or no intervention

Results for this comparison were mainly from a small trial comparing valproate versus placebo (Rickels 1999). Results showed a beneficial effect of valproate on benzodiazepine discontinuation at end of intervention (Analysis 1.1: 1 study, 27 participants; RR 2.55, 95% CI 1.08 to 6.03; GRADE: very low-quality evidence) and on benzodiazepine relapse at end of intervention (Analysis 1.2: 1 study, 27 participants; RR 0.31, 95% CI 0.11 to 0.90; GRADE: very low-quality evidence). However, there was no effect on benzodiazepine discontinuation at longest follow-up (Analysis 1.3: 1 study, 24 participants; RR 1.57, 95% CI 0.80 to 3.09; GRADE: very low-quality evidence), benzodiazepine relapse at longest follow-up (Analysis 1.4: 1 study, 24 participants; RR 0.43, 95% CI 0.13 to 1.39; GRADE: very low-quality evidence), or symptoms of anxiety at end of intervention (Analysis 1.5: 1 study, 27 participants; MD -0.40 points, 95% CI -6.47 to 5.67; GRADE: very low-quality evidence).

For benzodiazepine discontinuation, we calculated the required information size to be 1918 participants, using a control event proportion of 48%, a relative risk reduction of 20%, type I error of 2.5%, power of 90%, and a diversity of 30%. We could not perform Trial Sequential Analysis as there was only one trial.

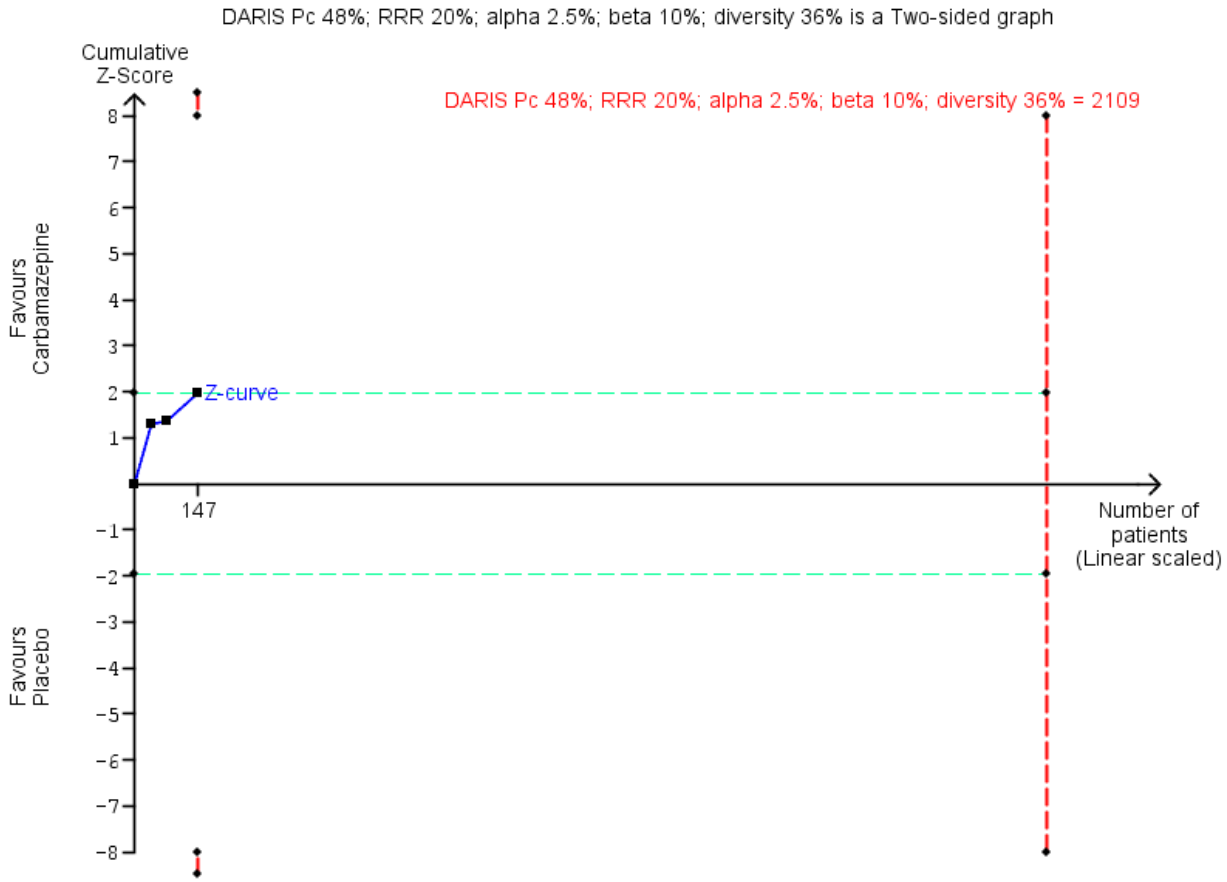
For benzodiazepine withdrawal symptoms, it was possible to perform a meta-analysis using data from Rickels 1999 and data from another small trial investigating benzodiazepine withdrawal in methadone maintenance users, Vorma 2011, comparing valproate versus no intervention. This meta-analysis indicated no difference between intervention groups (Analysis 1.6: 2 studies, 56 participants; SMD -0.15, 95% CI -0.68 to 0.37; GRADE: very low-quality evidence). Due to marked differences in among-participant variability, we did not re-express the SMD using one of the specific measurement instruments. Results were similar if analysing placebo or no intervention separately as control group.

Please see Summary of findings for the main comparison.

Carbamazepine versus placebo

Results for this comparison stem from three smaller trials (Di Costanzo 1992; Klein 1994; Schweizer 1991), not all of which contribute data to all outcomes. It was possible to perform a meta-analysis for benzodiazepine discontinuation at end of intervention, where no significant differences between groups were detected (Analysis 2.1: 3 studies, 147 participants; RR 1.33, 95% CI 0.99 to 1.80; GRADE: low quality-evidence). Trial Sequential Analysis showed that the diversity-adjusted required information size of 2109 participants was not reached, as the accrued number of participants was only 147 (7.0%), showing that insufficient information has been accrued (Figure 4).

Figure 4. Trial Sequential Analysis of comparison: 2 Carbamazepine versus placebo, outcome: 2.1 Benzodiazepine discontinuation. Trial Sequential Analysis on benzodiazepine discontinuation in three trials was performed based on the proportion with benzodiazepine discontinuation in the control group set at 48%, a relative risk reduction (RRR) of 20%, a type I error of 2.5%, a type II error of 10% (90% power), and diversity of 36% as observed in the trials. The diversity-adjusted required information size (DARIS) was 2109 participants, and the Trial Sequential Analysis-adjusted confidence interval is 0.24 to 2.38. The blue line represents the cumulative Z-score of the meta-analysis. The green lines represent the conventional statistical boundaries of P = 5%. The cumulative Z-curve (blue line) touches the conventional statistical boundaries, but does not cross the trial sequential monitoring boundaries, and the diversity-adjusted required information size is not met, showing that insufficient information has been accrued.



For benzodiazepine withdrawal symptoms, results did not favour carbamazepine (Analysis 2.2: 2 studies, 76 participants; SMD -1.14, 95% CI -2.43 to 0.16; GRADE: very low quality-evidence). Due to marked differences in among-participant variability, we did not re-express the SMD using one of the specific measurement instruments.

For the following outcomes, only data from single trials were available, finding no differences between groups regarding benzodiazepine discontinuation at longest follow-up (Analysis 2.3: 1 study, 40 participants; RR 1.41, 95% CI 0.86 to 2.29; GRADE: very low-quality evidence), relapse to benzodiazepine use (Analysis 2.4: 1 study, 36 participants; RR 0.33, 95% CI 0.08 to 1.44; GRADE: very low-quality evidence), and non-serious adverse events (Analysis 2.6: 1 study, 36 participants; RR 7.00, 95% CI 0.39 to 126.48; GRADE: very low-quality evidence). Data from a single trial found carbamazepine superior to placebo regarding symptoms of anxiety (Analysis 2.7: 1 study, 36 participants; MD -6.00 points, 95% CI -9.58 to -2.42; GRADE: very low-quality evidence).

When evaluating benzodiazepine withdrawal symptoms, the results were associated with significant heterogeneity. We could identify no obvious reason for this heterogeneity.

Please see Summary of findings 2.

Lithium versus placebo

One trial of moderate size investigated lithium versus placebo for benzodiazepine discontinuation and found no difference between groups regarding benzodiazepine discontinuation (Analysis 3.1: 1 study, 230 participants; RR 1.05, 95% CI 0.86 to 1.28; GRADE: low-quality evidence), non-serious adverse events (Analysis 3.3: 1 study, 230 participants; RR 1.06, 95% CI 0.75 to 1.49; GRADE: very low-quality evidence), and discontinuation due to adverse events

(Analysis 3.4: 1 study, 230 participants; RR 1.38, 95% CI 0.13 to 15.03; GRADE: very low-quality evidence) (Lecrubier 2005). Data on other outcomes specified in this review were not available.

For benzodiazepine discontinuation, we calculated the required information size to be 1918 participants, using a control event proportion of 48%, a relative risk reduction of 20%, type I error of 2.5%, power of 90%, and a diversity of 30%. We could not perform Trial Sequential Analysis as there was only one trial.

Please see Summary of findings 3.

Pregabalin versus placebo

One smaller trial investigated this comparison (Hadley 2012), finding no significant difference between groups regarding benzodiazepine discontinuation (Analysis 4.1: 1 study, 106 participants; RR 1.44, 95% CI 0.92 to 2.25; GRADE: very low-quality evidence), but finding superior effect of pregabalin regarding benzodiazepine withdrawal symptoms (Analysis 4.2; 1 study, 106 participants; MD -3.10 points, 95% CI -3.51 to -2.69; GRADE: very low-quality evidence) and symptoms of anxiety (Analysis 4.3: 1 study, 106 participants; MD -4.80 points, 95% CI -5.28 to -4.32; GRADE: very low-quality evidence). There were no differences between groups for serious and non-serious adverse events as well as for discontinuation due to side effects (Analysis 4.4; Analysis 4.5; Analysis 4.6).

For benzodiazepine discontinuation, we calculated the required information size to be 1918 participants, using a control event proportion of 48%, a relative risk reduction of 20%, type I error of 2.5%, power of 90%, and a diversity of 30%. We could not perform Trial Sequential Analysis as there was only one trial.

Please see Summary of findings 4.

Captodiame versus placebo

One smaller trial compared captodiame (an antihistamine used as a sedative and anxiolytic) with placebo and found that captodiame had a beneficial effect in terms of benzodiazepine withdrawal symptoms (Analysis 5.1: 1 study, 81 participants; MD -1.00 points, 95% CI -1.13 to -0.87; GRADE: very low-quality evidence) and symptoms of anxiety (Analysis 5.2: 1 study, 81 participants; MD -5.70 points, 95% CI -6.05 to -5.35) (Mercier-Guyon 2004). Data on other outcomes specified in this review were not available.

For benzodiazepine withdrawal symptoms assessed with the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ), we calculated the required information size to be 229 participants, using a variance of 20 points, a minimal relative difference of 2.25 points, type I error of 2.5%, power of 90%, and a diversity of 30%. We could not perform Trial Sequential Analysis as there was only one trial.

Please see Summary of findings 5.

Paroxetine versus placebo or no intervention

Three smaller trials evaluated paroxetine to facilitate benzodiazepine discontinuation: two versus placebo, GlaxoSmithKline 2002; Zitman 2001, and one versus no intervention (Nakao 2006). It was possible to perform a meta-analysis for the following outcomes, where placebo and no intervention were pooled as control group.

- Benzodiazepine discontinuation at end of intervention, where no intervention effect could be found (Analysis 6.1: 3 studies, 221 participants; RR 1.45, 95% CI 0.88 to 2.39; GRADE: very low-quality evidence). Trial Sequential Analysis showed that the diversity-adjusted required information size of 9448 participants was not reached, as the accrued number of participants was only 210 (2.34%), showing that insufficient information has been obtained (Figure 5). Results for benzodiazepine discontinuation were associated with significant heterogeneity (Analysis 6.1), for which we could not identify any obvious reason.
- Benzodiazepine withdrawal symptoms at end of intervention, assessed with BWSQ, indicated a difference in favour of paroxetine (Analysis 6.2: 2 studies, 99 participants; MD -3.57 points, 95% CI -5.34 to -1.80; GRADE: very low-quality evidence). Trial Sequential Analysis based on a minimal relevant clinical difference of 2.25 points, variance of 20 (empirical data), a type I error of 1.25%, a type II error of 10% (90% power), and diversity of 0% showed that the diversity-adjusted required information size of 229 participants was not met (Figure 6). However, the cumulative Z-curve touched the trial sequential monitoring boundaries for benefit, indicating that sufficient information had been obtained, and that the result was not due to random error.
- Symptoms of anxiety, assessed with Hamilton Anxiety Rating Scale (HAM-A), indicated a difference in favour of paroxetine (Analysis 6.3: 2 studies, 99 participants; MD -6.75 points, 95% CI -9.64 to -3.86; GRADE: very low-quality evidence). We performed Trial Sequential Analysis on anxiety, assessed with HAM-A, with a minimal relevant clinical difference of 5 points, variance of 103 points, based on a type I error of 1.25%, a type II error of 10% (90% power), and diversity of 0% (Figure 7). The diversity-adjusted required information size of 236 participants was not met. However, the cumulative Z-curve crossed the trial sequential monitoring boundaries for benefit, indicating that sufficient information had been obtained, and that the result was not due to random error.

Figure 5. Trial Sequential Analysis of comparison: 6 Paroxetine versus placebo, outcome: 6.1 Benzodiazepine discontinuation. Trial Sequential Analysis on benzodiazepine discontinuation in three trials was performed based on the proportion with benzodiazepine discontinuation in the control group set at 48%, a relative risk reduction of 20%, a type I error of 2.5%, a type II error of 10% (90% power), and diversity of 86% as observed in the trials. The diversity-adjusted required information size was 9448 participants, and the Trial Sequential Analysis-adjusted confidence interval could not be estimated due to lack of information. The blue line represents the cumulative Z-score of the meta-analysis. The green lines represent the conventional statistical boundaries of P = 5%. The cumulative Z-curve (blue line) does not cross the conventional statistical boundaries. The trial sequential monitoring boundaries and the diversity-adjusted required information size are not shown as the accrued number of participants only amounted to 221/9448 (2.34%), showing that insufficient information has been accrued.

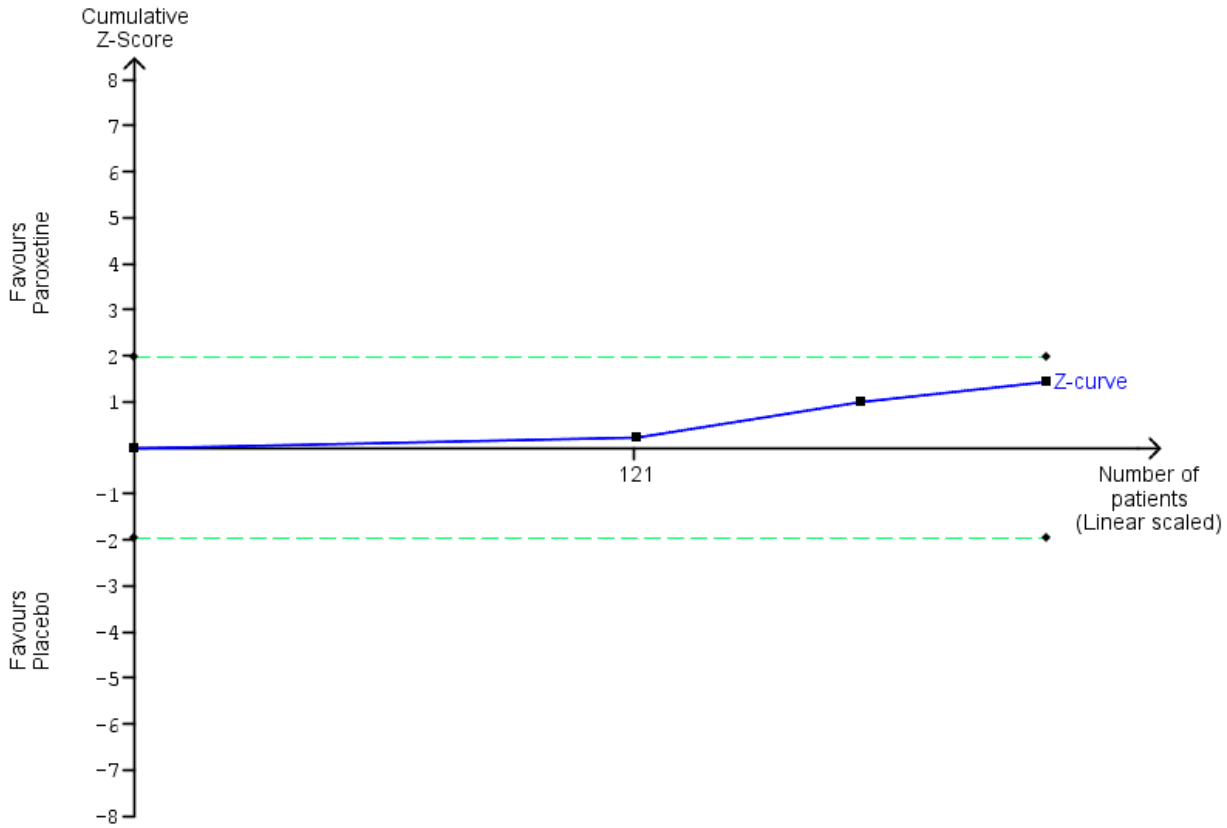


Figure 6. Trial Sequential Analysis of comparison: 6 Paroxetine versus placebo, outcome: 6.2 Benzodiazepine withdrawal symptoms Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ). Trial Sequential Analysis on benzodiazepine withdrawal symptoms assessed with BWSQ assessing a minimal relevant clinical difference (MIREDIF) of 2.25 points, and a variance of 20 points (empirical data), was performed based on a type I error of 1.25%, a type II error of 10% (90% power), and diversity of 0%. The diversity-adjusted required information size (DARIS) was 229 participants, and the Trial Sequential Analysis-adjusted confidence interval is -7.18 to 0.05. The blue line represents the cumulative Z-score of the meta-analysis. The green lines represent the conventional statistical boundaries of P = 0.05. The red inward-sloping lines represent the trial sequential monitoring boundaries. The cumulative Z-curve touches the trial sequential monitoring boundaries, indicating that sufficient information was provided.

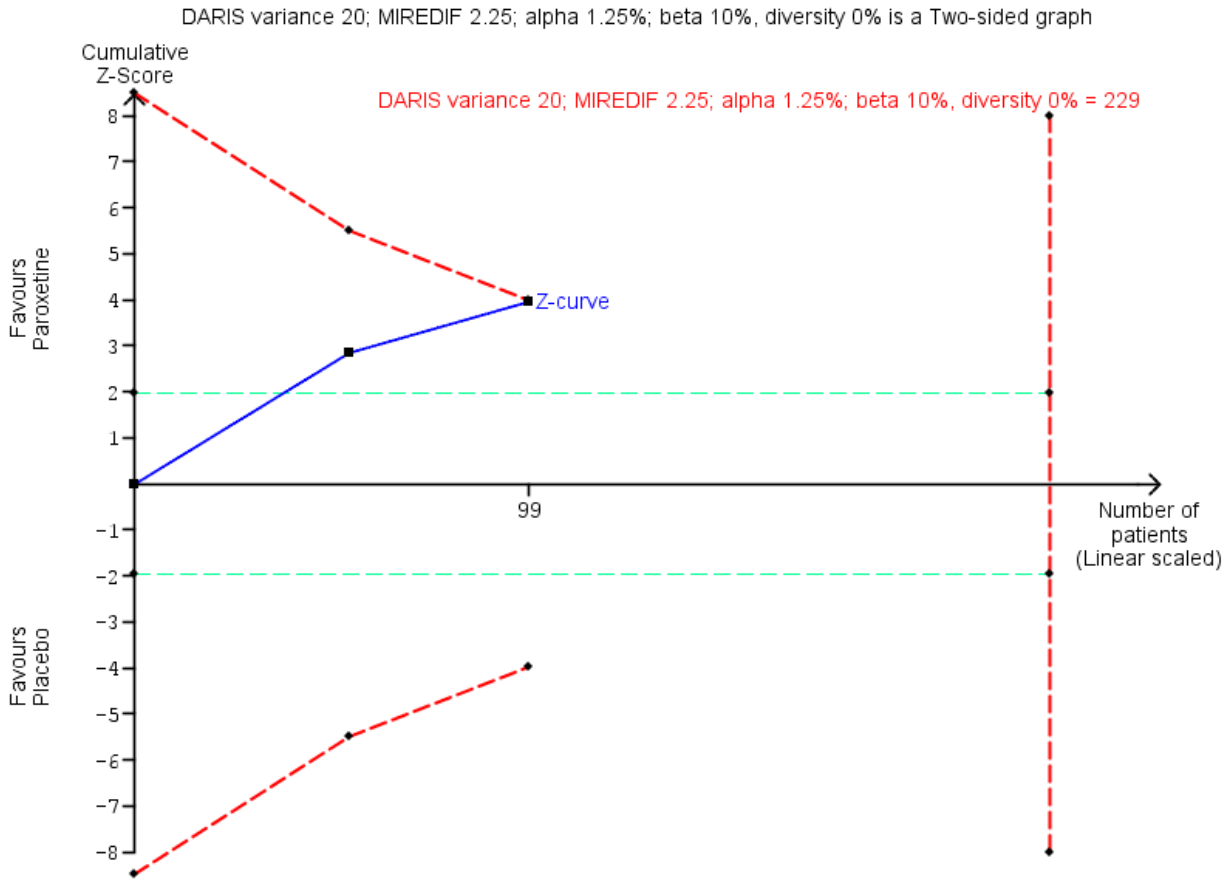
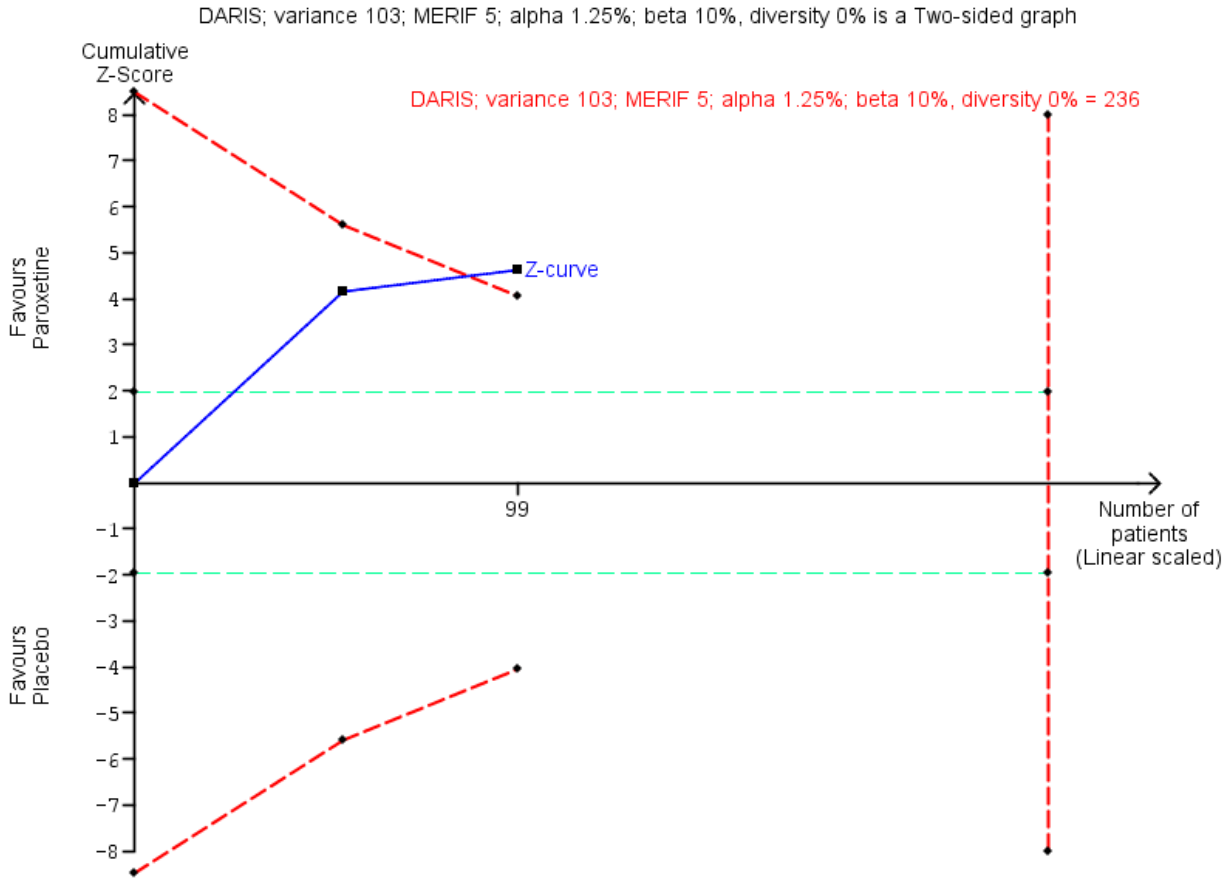


Figure 7. Trial Sequential Analysis of comparison: 6 Paroxetine versus placebo, outcome: 6.3 Anxiety, Hamilton Anxiety Rating Scale (HAM-A). Trial Sequential Analysis on anxiety evaluated with HAM-A assessing a minimal relevant clinical difference (MIREDIF) of 5 points, and a variance of 103 points, was performed based on a type I error of 1.25%, a type II error of 10% (90% power), and diversity of 0%. The diversity-adjusted required information size (DARIS) was 236 participants, and the Trial Sequential Analysis-adjusted confidence interval is -12.72 to -0.80. The blue line represents the cumulative Z-score of the meta-analysis. The green lines represent the conventional statistical boundaries of P = 0.05. The red inward-sloping lines represent the trial sequential monitoring boundaries. The cumulative Z-curve crosses the trial sequential monitoring boundaries, indicating that sufficient information was provided.



Results were similar if analysing placebo or no intervention separately as control group.

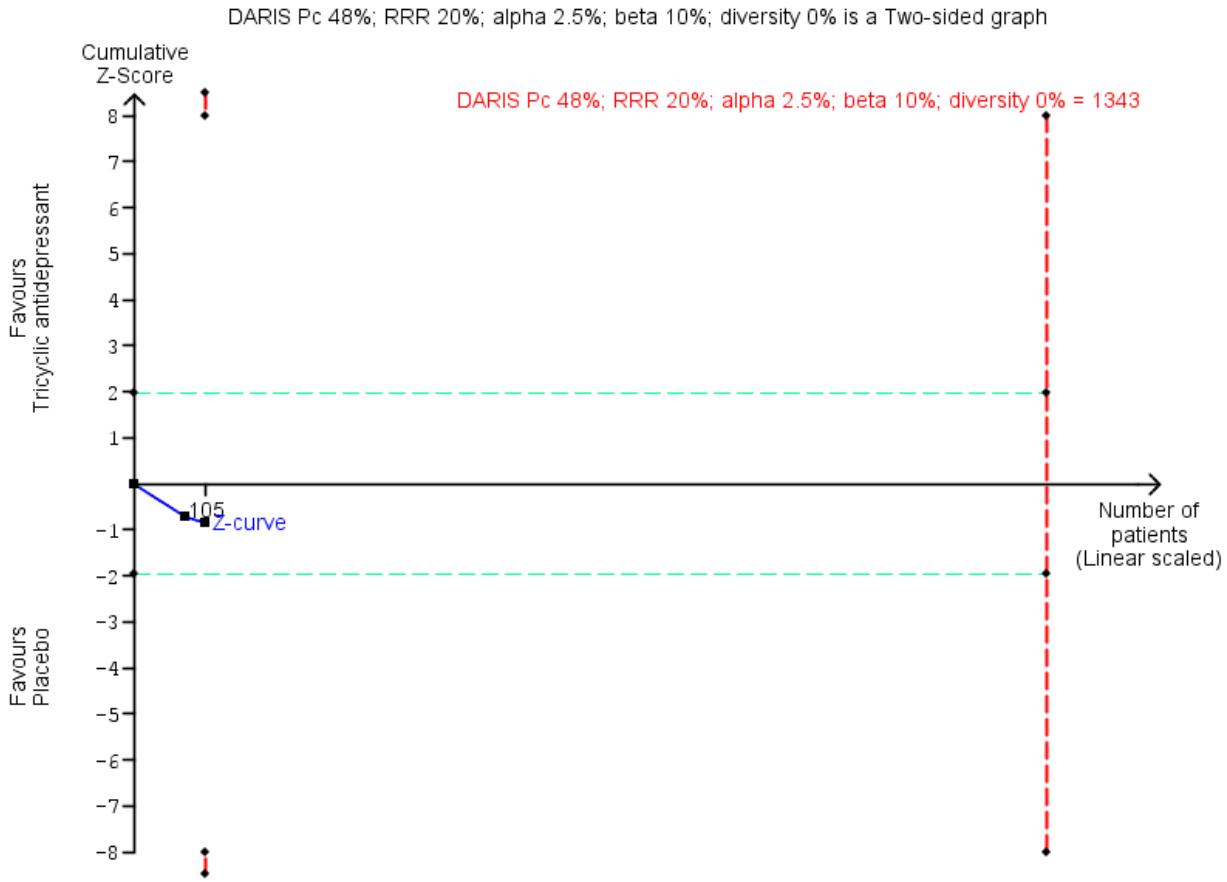
One trial evaluated benzodiazepine withdrawal symptoms at longest follow-up, where no effect of paroxetine could be found (Analysis 6.4: 1 study, 54 participants; MD -0.13 points, 95% CI -4.03 to 3.77; GRADE: very low-quality evidence). For non-serious adverse events, no differences between intervention groups were found (Analysis 6.6).

Please see Summary of findings 6.

Tricyclic antidepressants (dosulepin, imipramine, or trazodone) versus placebo

Four trials, each with a small sample size, investigated tricyclic antidepressants versus placebo (Rickels 2000; Rynn 2003; Tyrer 1996; Zhang 2013). It was possible to perform a meta-analysis for benzodiazepine discontinuation at end of intervention, where results showed no difference between intervention groups (Analysis 7.1: 2 studies, 105 participants; RR 0.82, 95% CI 0.52 to 1.28; GRADE: very low-quality evidence). Trial Sequential Analysis showed that the diversity-adjusted required information size of 1343 participants was not reached, as the accrued number of participants was only 105 (7.81%), indicating that insufficient information has been obtained (Figure 8).

Figure 8. Trial Sequential Analysis of comparison: 7 Tricyclic antidepressants versus placebo, outcome: 7.1 Benzodiazepine discontinuation. Trial Sequential Analysis on benzodiazepine discontinuation in two trials was performed based on the proportion with benzodiazepine discontinuation in the control group set at 48%, a relative risk reduction (RRR) of 20%, a type I error of 2.5%, a type II error of 10% (90% power), and diversity of 0% as observed in the trials. The diversity-adjusted required information size (DARIS) was 1343 participants, and the Trial Sequential Analysis-adjusted confidence interval is 0.20 to 7.55. The blue line represents the cumulative Z-score of the meta-analysis. The green lines represent the conventional statistical boundaries of P = 5%. The cumulative Z-curve (blue line) does not cross the conventional statistical boundaries or the trial sequential monitoring boundaries (red dotted lines), and the diversity-adjusted required information size is not met, showing that insufficient information has been accrued.



Two trials reported symptoms of anxiety (Rynn 2003; Zhang 2013), with no difference between intervention groups (Analysis 7.2: 2 studies, 66 participants; MD -10.38 points, 95% CI -25.96 to 5.20; GRADE: very low-quality evidence). These data were associated with significant heterogeneity, the reason for which was that the Chinese study, Zhang 2013, reported results that were far more positive in favour of the experimental drug than the remainder of the included trials.

The following outcomes were reported in one trial each: benzodiazepine discontinuation at longest follow-up, showing a beneficial effect of tricyclic antidepressants (Analysis 7.3: 1 study, 47 participants; RR 2.20, 95% CI 1.27 to 3.82; GRADE: low-quality evidence); benzodiazepine withdrawal symptoms (Analysis 7.4: 1 study, 38 participants; MD -19.78 points, 95% CI -20.25 to -19.31; GRADE: very low-quality evidence) with a significant difference between groups in favour of tricyclic antidepressants; relapse to benzodiazepine use, showing no intervention effect (Analysis 7.5: 1 study, 36 participants; RR 2.00, 95% CI 0.73 to 5.47); and discontinuation due to adverse events, also showing no intervention effect (Analysis 7.6: 2 studies, 134 participants; RR 1.16, 95% CI 0.42 to 3.21; GRADE: very low-quality evidence).

Please see Summary of findings 7.

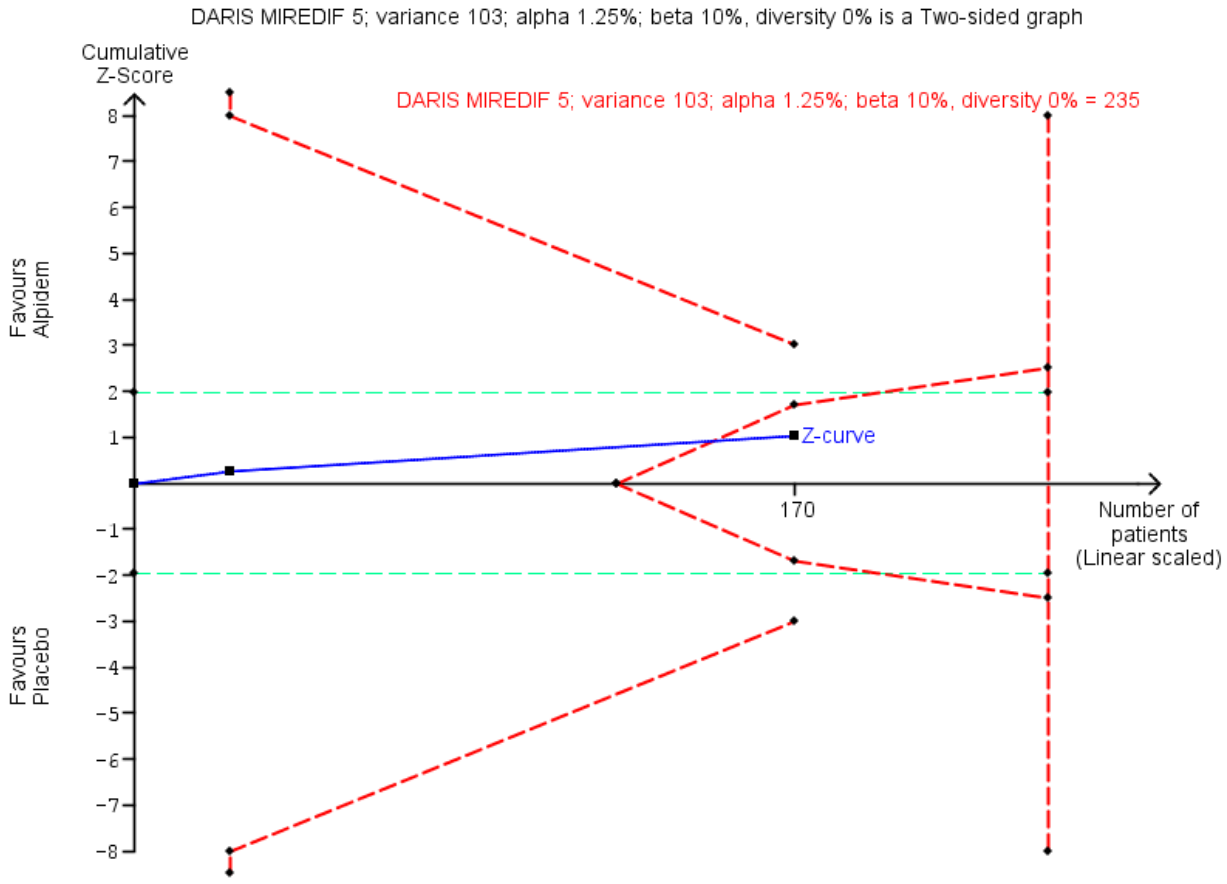
Alpidem versus placebo

Two smaller trials compared alpidem (an anxiolytic drug from the imidazopyridine family) with placebo for benzodiazepine discontinuation (Cassano 1996; Lader 1993), showing a disadvantage of alpidem for this outcome at end of intervention (Analysis 8.1: 1 study, 25 participants; RR 0.41, 95% CI 0.17 to 0.99; NNTH 2.3 participants; GRADE: low-quality evidence). We calculated the required information size to be 1918 participants, using a control event proportion of 48%, a relative risk reduction

of 20%, type I error of 2.5%, power of 90%, and a diversity of 30%. Withdrawal syndrome was also analysed, suggesting a disadvantage of alpidem (Analysis 8.2: 1 study, 145 participants; RR 4.86, 95% CI 1.12 to 21.14; NNTH 5.9 participants; GRADE: low-quality evidence). We calculated the required information size to be 9202 participants, using a control event proportion of 15%, a relative risk reduction of 20%, type I error of 2.5%, power of 90%, and a diversity of 30%. We could not perform Trial Sequential Analysis for either of these outcomes because they were only reported in one trial.

It was possible to perform a meta-analysis for symptoms of anxiety, as assessed by HAM-A, where no intervention effect was found (Analysis 8.3: 2 studies, 170 participants; MD -1.60 points, 95% CI -4.64 to 1.45; GRADE: low-quality evidence). In Trial Sequential Analysis using a minimal relevant clinical difference of 5 points, variance of 103 points, type I error of 1.25%, type II error of 10% (90% power), and diversity of 0% (Figure 9), we found that the diversity-adjusted required information size of 235 participants was not met. However, the cumulative Z-curve crossed the beta-spending (futility) boundaries, indicating that an intervention effect, if any, was less than 5 points.

Figure 9. Trial Sequential Analysis of comparison: 8 Alpidem versus placebo, outcome: 8.3 Anxiety, Hamilton Anxiety Rating Scale (HAM-A). Trial Sequential Analysis on anxiety evaluated with HAM-A assessing a minimal relevant clinical difference (MIREDIF) of 5 points, and a variance of 103 points (empirical data), was performed based on a type I error of 1.25%, a type II error of 10% (90% power), and diversity of 0%. The diversity-adjusted required information size (DARIS) was 235 participants, and the Trial Sequential Analysis-adjusted confidence interval is -6.28 to 3.08. The blue line represents the cumulative Z-score of the meta-analysis. The green lines represent the conventional statistical boundaries of P = 0.05. The red inward-sloping lines represent the trial sequential alpha-spending monitoring boundaries, while the red outward-sloping lines represent the beta-spending (futility) boundaries. The cumulative Z-curve crosses the beta-spending (futility) boundaries, showing that an intervention effect, if any, is less than 5 points.



One trial reported relapse to benzodiazepine use, suggesting no intervention effect (Analysis 8.4: 1 study, 145 participants; RR 0.33, 95% CI 0.09 to 1.20; GRADE: very low-quality evidence).

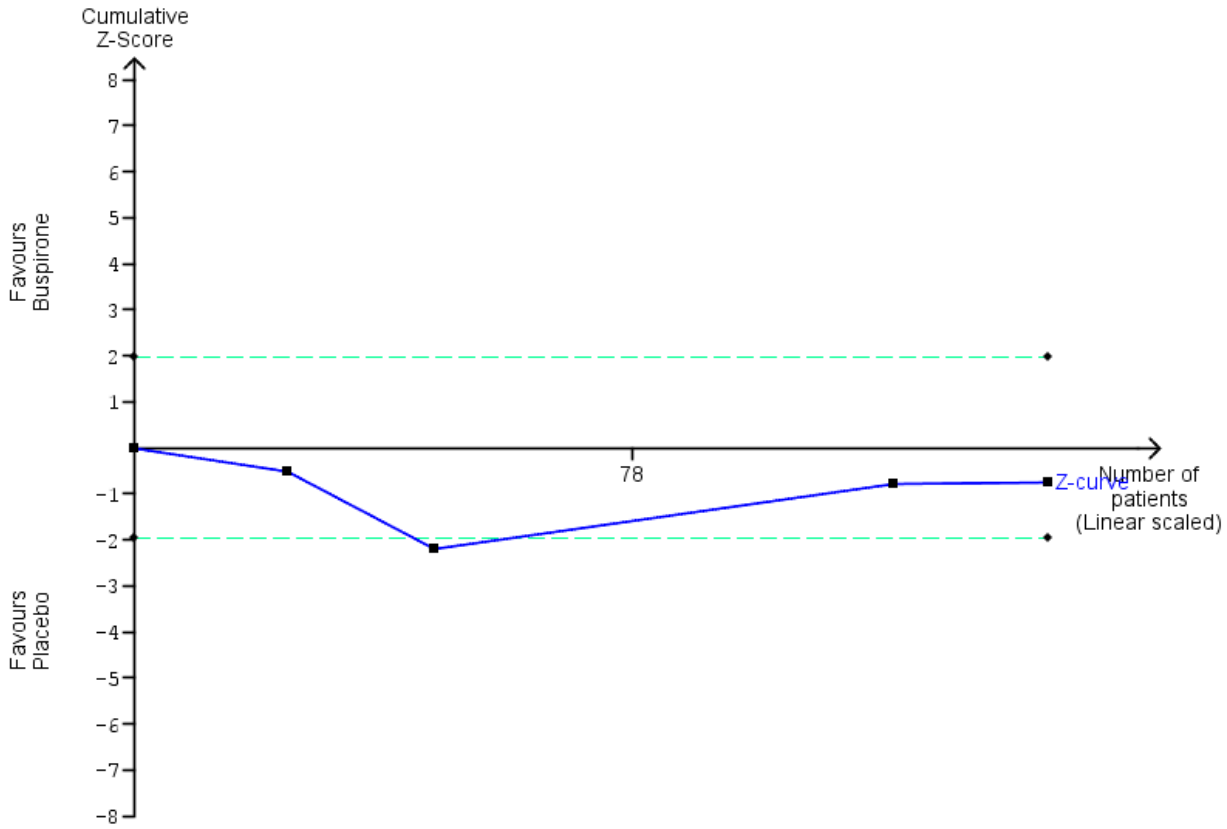
Please see Summary of findings 8.

Buspirone versus placebo

Four trials examined use of buspirone compared with placebo (Ashton 1990; Lader 1987; Morton 1995; Udelman 1990), each with a small sample size. It was possible to perform a meta-analysis with

regard to benzodiazepine discontinuation at end of intervention, finding no difference between intervention groups (Analysis 9.1: 4 studies, 143 participants; RR 0.82, 95% CI 0.49 to 1.37; GRADE: low-quality evidence). Trial Sequential Analysis showed that the diversity-adjusted required information size of 3381 participants was not reached, as the accrued number of participants was only 143 (4.23%), showing that insufficient information has been accrued (Figure 10).

Figure 10. Trial Sequential Analysis of comparison: 9 Buspirone versus placebo, outcome: 9.1 Benzodiazepine discontinuation. Trial Sequential Analysis on benzodiazepine discontinuation in four trials was performed based on the proportion with benzodiazepine discontinuation in the control group set at 48%, a relative risk reduction of 20%, a type I error of 2.5%, a type II error of 10% (90% power), and diversity of 60% as observed in the trials. The diversity-adjusted required information size was 3381 participants, and the Trial Sequential Analysis-adjusted confidence interval could not be estimated due to lack of information. The blue line represents the cumulative Z-score of the meta-analysis. The green lines represent the conventional statistical boundaries of P = 5%. The cumulative Z-curve (blue line) does not cross the conventional statistical boundaries. The trial sequential monitoring boundaries and the diversity-adjusted required information size are not shown, as the accrued number of participants only amounted to 143/3381 (4.23%), showing that insufficient information has been accrued.



There was also no intervention effect for anxiety symptoms at end of intervention (Analysis 9.2: 2 studies, 41 participants; SMD 0.18, 95% CI -0.50 to 0.86; GRADE: very low-quality evidence).

The following outcomes were reported in only one trial each and with no sign of intervention effect: benzodiazepine withdrawal symptoms at end of intervention (Analysis 9.3: 1 study, 17 participants; MD 4.69 points, 95% CI -14.47 to 23.85; GRADE: very low-quality evidence), benzodiazepine discontinuation at longest follow-up (Analysis 9.4: 1 study, 23 participants; RR 0.60, 95% CI 0.34 to 1.05; GRADE: low-quality evidence), benzodiazepine withdrawal symptoms at longest follow-up (Analysis 9.5: 1 study, 15 participants; MD -1.34 points, 95% CI -14.31 to 11.63; GRADE: very low-quality evidence), and symptoms of anxiety at longest follow-up (Analysis 9.6: 1 study, 12 participants; MD 2.75 points, 95% CI -2.83 to 8.33; GRADE: very low-quality evidence). Due to marked differences in among-participant variability, we did not re-express the SMD using one of the specific measurement instruments.

Results for benzodiazepine discontinuation (Analysis 9.1) were associated with significant heterogeneity, with the most marked differences between Ashton 1990 (more in favour of placebo or no difference between groups) and Udelman 1990 (more in favour

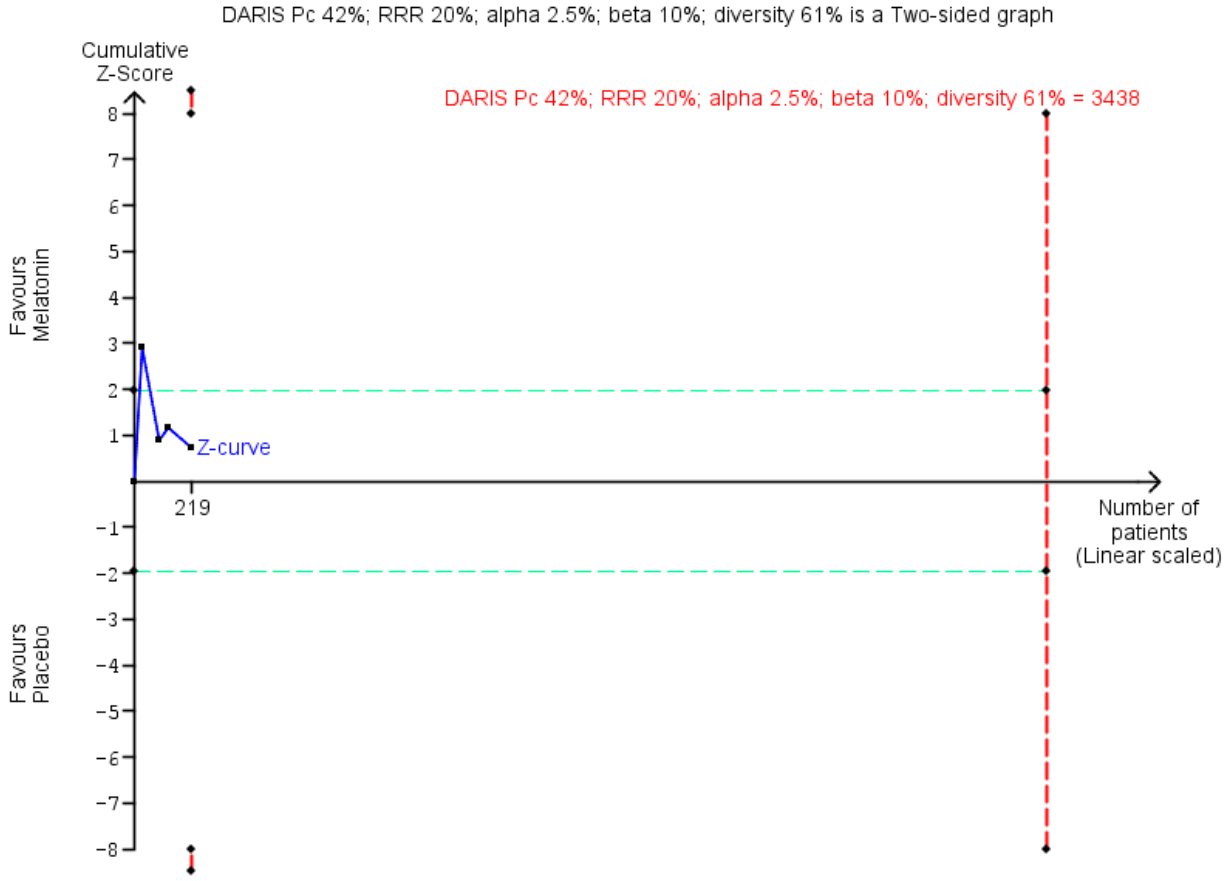
of buspirone). We could not identify any obvious reasons for the observed heterogeneity.

Please see Summary of findings 9.

Melatonin versus placebo

Four trials of small to moderate sample size investigated melatonin (both short-acting and prolonged release formulation) versus placebo for benzodiazepine discontinuation at end of intervention (Baandrup 2016; Garfinkel 1999; Peles 2007; Vissers 2007). It was possible to perform a meta-analysis for benzodiazepine discontinuation at end of intervention, which showed no difference between intervention groups (Analysis 10.1: 4 studies, 219 participants; RR 1.20, 95% CI 0.73 to 1.96; GRADE: very low-quality evidence). Trial Sequential Analysis showed that the diversity-adjusted required information size of 3438 participants was not reached, as the accrued number of participants was only 219 (6.37%), showing that insufficient information has been accrued (Figure 11).

Figure 11. Trial Sequential Analysis of comparison: 10 Melatonin versus placebo, outcome: 10.1 Benzodiazepine discontinuation. Trial Sequential Analysis on benzodiazepine discontinuation in four trials was performed based on the proportion with benzodiazepine discontinuation in the control group set at 48%, a relative risk reduction (RRR) of 20%, a type I error of 2.5%, a type II error of 10% (90% power), and diversity of 61% as observed in the trials. The diversity-adjusted required information size (DARIS) was 3438 participants, and the Trial Sequential Analysis-adjusted confidence interval is 0.11 to 6.25. The blue line represents the cumulative Z-score of the meta-analysis. The green lines represent the conventional statistical boundaries of P = 5%. The cumulative Z-curve (blue line) does not cross the conventional statistical boundaries or the trial sequential monitoring boundaries (red dotted lines), and the diversity-adjusted required information size is not met, showing that insufficient information has been accrued.



We found no intervention effect likewise for insomnia (Analysis 10.2: 3 studies, 150 participants; SMD -1.23, 95% CI -2.70 to 0.23; GRADE: very low-quality evidence) or discontinuation due to adverse events (Analysis 10.3: 2 studies, 120 participants; RR 2.10, 95% CI 0.20 to 22.26; GRADE: very low-quality of evidence). The following outcomes were reported in one trial each: benzodiazepine discontinuation at longest follow-up, showing no intervention effect (Analysis 10.4: 1 study, 38 participants; RR 1.03, 95% CI 0.47 to 2.27; GRADE: very low-quality evidence), adverse events, with no intervention effect (Analysis 10.5: 1 study, 86 participants; RR 0.97, 95% CI 0.52 to 1.82; GRADE: very low-quality evidence), and relapse to benzodiazepine use, also with

no indication of intervention effect (Analysis 10.6: 1 study, 38 participants; RR 1.80, 95% CI 0.37 to 8.68; GRADE: very low-quality evidence).

When evaluating insomnia, the results were associated with significant heterogeneity; this was explained by Garfinkel 1999, which showed a markedly significant result in favour of melatonin, whereas the two other the trials included in this meta-analysis showed no or a much smaller difference between intervention groups (Baandrup 2016; Peles 2007). We could not identify any obvious reason for this observed heterogeneity, other than Garfinkel 1999 being the only one of these studies involved with a pharmaceutical company.

Please see Summary of findings 10.

Flumazenil versus placebo

Three small trials examined whether flumazenil can aid in benzodiazepine discontinuation (Gerra 1993; Gerra 2002; Harrison-Read 1996). It was possible to perform a meta-analysis for benzodiazepine withdrawal symptoms at end of intervention, which showed a beneficial effect of flumazenil (Analysis 11.1: 3 studies, 58 participants; SMD -0.95, 95% CI -1.71 to -0.19; GRADE: very low-quality evidence). Due to marked differences in among-participant variability, we did not re-express the SMD using one of the specific measurement instruments. We could not calculate the required information size because the trials did not use the same instrument, and results were reported using SMD.

The following outcomes were reported in one trial each: symptoms of anxiety, with results in favour of flumazenil (Analysis 11.2: 1 study, 18 participants; MD -1.30 points, 95% CI -2.28 to -0.32; GRADE: very low-quality evidence) and benzodiazepine mean dose at end of intervention, with no difference between groups (Analysis 11.3: 1 study, 10 participants; MD -3.70 points, 95% CI -22.06 to 14.66; GRADE: very low-quality evidence). As previously noted, one of the flumazenil studies was ended prematurely due to severe withdrawal symptoms elicited during the trial procedure (Harrison-Read 1996).

When evaluating benzodiazepine withdrawal symptoms, the results were associated with significant heterogeneity for which no obvious reason could be identified.

Please see Summary of findings 11.

Propranolol versus placebo

One small trial evaluated propranolol versus placebo (Tyrer 1981). Only data on relapse to benzodiazepine use at end of intervention were available, showing no effect of the study intervention (Analysis 12.1: 1 study, 40 participants; RR 0.64, 95% CI 0.31 to 1.30; GRADE: very low-quality evidence).

Progesterone versus placebo

One small trial evaluated this comparison (Schweizer 1995), reporting no intervention effect on benzodiazepine discontinuation at end of intervention (Analysis 13.1: 1 study, 35 participants; RR 1.15, 95% CI 0.52 to 2.54; GRADE: very low-quality evidence), and a difference between groups in favour of placebo for non-serious adverse events (Analysis 13.2: 1 study, 35 participants; RR 3.13, 95% CI 1.15 to 8.54; GRADE: very low-quality evidence).

For benzodiazepine discontinuation, we calculated the required information size to be 1918 participants, using a control event proportion of 48%, a relative risk reduction of 20%, type I error of 2.5%, power of 90%, and a diversity of 30%. We could not perform Trial Sequential Analysis as there was only one trial.

Please see Summary of findings 12.

Magnesium aspartate versus placebo

One moderately sized trial compared magnesium aspartate (a mineral supplement) with placebo (Hantouche 1998), and found a beneficial effect of placebo for benzodiazepine discontinuation (Analysis 14.1: 1 study, 144 participants; RR 0.80, 95% CI 0.66 to 0.96; NNTH 5.8; GRADE: very low-quality evidence), but no difference between groups for symptoms of anxiety (Analysis 14.2: 1 study, 144 participants; MD -0.80 points, 95% CI -2.73 to 1.13; GRADE: very low-quality evidence), benzodiazepine relapse (Analysis 14.3: 1 study, 144 participants; RR 0.93, 95% CI 0.46 to 1.87; GRADE: very low-quality evidence), non-serious adverse events (Analysis 14.4: 1 study, 144 participants; RR 0.49, 95% CI 0.18 to 1.35; GRADE: very low-quality evidence), and discontinuation due to adverse events (Analysis 14.5: 1 study, 144 participants; RR 0.40, 95% CI 0.13 to 1.18; GRADE: very low-quality evidence).

For benzodiazepine discontinuation, we calculated the required information size to be 1918 participants, using a control event proportion of 48%, a relative risk reduction of 20%, type I error of 2.5%, power of 90%, and a diversity of 30%. We could not perform Trial Sequential Analysis because there was only one trial.

Please see Summary of findings 13.

Homeopathic drugs versus placebo

One small trial compared two homeopathic drugs ("Homéogène 46" and "Sédatif PC") versus placebo (Cialdella 2001), from which it was only possible to extract data on benzodiazepine discontinuation. When combining the homeopathic drugs as one experimental group versus placebo, the results showed no intervention effect (Analysis 15.1: 1 study, 51 participants; RR 0.79, 95% CI 0.36 to 1.70; GRADE: very low-quality evidence).

For benzodiazepine discontinuation, we calculated the required information size to be 1918 participants, using a control event proportion of 48%, a relative risk reduction of 20%, type I error of 2.5%, power of 90%, and a diversity of 30%. We could not perform Trial Sequential Analysis as there was only one trial.

Please see Summary of findings 14.

Carbamazepine versus tricyclic antidepressant (tianeptine)

Only one trial examined this comparison (Kornowski 2002), finding no additional effect of carbamazepine compared with tricyclic antidepressant for benzodiazepine discontinuation at end of intervention (Analysis 16.1: 1 study, 48 participants; RR 1.00, 95% CI 0.78 to 1.29; GRADE: low-quality evidence) and relapse to benzodiazepine use (Analysis 16.2: 1 study, 48 participants; RR 1.00, 95% CI 0.28 to 3.54; GRADE: low-quality evidence). Data on other outcomes specified in this review were not available.

Please see Summary of findings 15.

Bromazepam versus cyamemazine

One moderately sized trial examined bromazepam versus cyamemazine (a first-generation antipsychotic drug of the phenothiazine class with anxiolytic efficacy) (Lemoine 2006), reporting a difference in favour of cyamemazine for relapse to benzodiazepine use (Analysis 17.1: 1 study, 124 participants; RR 0.33, 95% CI 0.14 to 0.78; GRADE: very low-quality evidence), but no difference between groups for symptoms of anxiety (Analysis 17.2: 1 study, 160 participants; MD 0.50 points, 95% CI -1.23 to 2.23) or discontinuation due to adverse events (Analysis 17.3: 1 study, 160 participants; RR 2.87, 95% CI 0.79 to 10.44; GRADE: very low-quality evidence). We identified a difference in favour of bromazepam for non-serious adverse events (Analysis 17.4: 1 study, 160 participants; RR 1.68, 95% CI 1.01 to 2.78; GRADE: very low-quality evidence).

Zopiclone versus flunitrazepam

One small trial examined zopiclone (a short-acting benzodiazepine-like drug) versus flunitrazepam (a potent intermediate-acting benzodiazepine, which in many countries is no longer in use due to severe side effects) (Pat-Horenczyk 1998), finding no indication of intervention effect for relapse to benzodiazepine use (Analysis 18.1: 1 study, 18 participants; RR 1.05, 95% CI 0.23 to 4.78; GRADE: very low-quality evidence). Data on other outcomes specified in this review were not available.

Ondansetron, atenolol, and gabapentin

As described above, we were not able to extract data from three trials: Romach 1998 (ondansetron versus placebo), Saul 1989 (atenolol versus placebo), and Mariani 2016 (gabapentin versus placebo). None of these trials reported any effect on applied outcome measures of the respective experimental drug.

Adverse events

In general, adverse events were insufficiently reported, making it difficult to reliably assess the tolerability and safety of the investigated compounds.

DISCUSSION

Summary of main results

We included 38 trials in this review, but were able to extract data from only 35 trials investigating a total of 18 different comparisons for the primary outcome of benzodiazepine discontinuation. Valproate and tricyclic antidepressants seemed to have a potentially positive effect on benzodiazepine discontinuation, whereas withdrawal symptoms seemed to be potentially ameliorated by pregabalin, captodiame, paroxetine, tricyclic antidepressants, and flumazenil. The following pharmacological agents seemed to potentially reduce symptoms of anxiety: carbamazepine, pregabalin, captodiame, paroxetine, and flumazenil. However, flumazenil seemed to be associated with a high risk of precipitating a severe withdrawal syndrome, since one of the trials was prematurely ended due to observation of unacceptable adverse events (severe panic reactions). Alpidem seemed to worsen both the probability of discontinuing benzodiazepines and the intensity of withdrawal symptoms and should not be further investigated for this use. Likewise, magnesium aspartate seemed to decrease the proportion of participants discontinuing benzodiazepines.

Overall completeness and applicability of evidence

A plethora of different drugs have been investigated in a number of small trials, many of which are of questionable quality, poorly reported, and thus difficult to extract data from. The data set is therefore not complete, but nevertheless judged by the review authors to give a full representation of the current body of evidence in this area. A substantial proportion of included trials were initiated and sponsored by the pharmaceutical industry.

Quality of the evidence

We generally rated the quality of the evidence as very low or low, representing small studies of generally poor methodology and poor reporting. Especially as many of the trials were of older date, modern standards of design and reporting were not fulfilled. As a result, the conclusions of this review should be considered tentative at best. Nonetheless, the review provides an overview of the current status of evidence and points to future directions for research on the development of pharmacotherapies for benzodiazepine dependence.

Potential biases in the review process

Some of the authors of this review also authored one of the included trials (Baandrup 2016). Data extraction and risk of bias assessment of this particular trial was done by LB and JR, the latter of whom was not involved in the trial in any way. The trial examined melatonin for benzodiazepine discontinuation. The meta-analysis showed no benefit of melatonin for any of the reported outcomes, and thus we do not believe that our involvement in one the included trials in any way biased the results.

In our protocol, we planned to only focus our assessments on randomised controlled trials (Baandrup 2015). By doing so, we are well aware of the fact that we put an overemphasis on potential beneficial effects of the assessed interventions and ran the risks of overlooking harms. The reasons for these considerations are that harms are generally not well reported in randomised controlled trials, and that observational studies are usually needed to detect rare- and late-occurring adverse events (Ioannidis 2004; Ioannidis 2009).

We did not search relevant databases of regulatory authorities as this was not planned in our protocol. We could therefore have overlooked relevant trials that have not been published in the usual literature. In all likelihood, such trials are at high risk of showing neutral or negative intervention effects, but for completeness of literature searches such databases of regulatory authorities need to be searched in future updates of this review (Schroll 2015).

Agreements and disagreements with other studies or reviews

A number of other reviews have been published on similar topics. A Cochrane Review investigating pharmacological interventions for benzodiazepine mono-dependence management in outpatient settings in 35 studies pointed to a potential value of carbamazepine, but concluded that larger, controlled studies were needed (Denis 2006). The current review confirms the potential value of carbamazepine, but the body of evidence is too weak to translate this into a clinical recommendation.

Voshaar 2006 found that augmentation of systematic benzodiazepine discontinuation with imipramine was superior to systematic discontinuation alone. This conclusion is in agreement with the current review, although we could only identify a possible beneficial effect of tricyclic antidepressant on benzodiazepine discontinuation at longest follow-up, based on data from a single trial. Furthermore, we report a potential favour of tricyclic antidepressants regarding benzodiazepine withdrawal symptoms, but this was also based on only one trial with results that generally seemed biased.

In Parr 2009, gradual dose reduction plus substitutive pharmacotherapies was compared with gradual dose reduction alone, restricted to general practice and outpatient settings. An evaluation of benzodiazepine cessation rate in 18 studies found promise for a few substitutive pharmacotherapies (melatonin, paroxetine, trazodone, and valproate), but concluded that the current evidence was insufficient to support their use. Our review, which included several more studies, adds further value to the suggestion of further investigating this topic, potentially involving paroxetine (and/or other selective serotonin reuptake inhibitors (SSRIs)) and valproate.

Darker 2015 examined psychosocial interventions for benzodiazepine withdrawal, finding a short-term beneficial effect of cognitive behavioural therapy that did not last beyond three months. Motivational interviewing had no effect on benzodiazepine discontinuation. Other promising interventions investigated in single trials included a tailored letter from the general practitioner, standardised interview, and relaxation technique. The evidence base for using non-pharmacological interventions to facilitate benzodiazepine use is unfortunately thus not much more convincing than the evidence gathered in the current review on pharmacological interventions.

AUTHORS' CONCLUSIONS

Implications for practice

The current systematic review with meta-analysis and Trial Sequential Analysis could not find any pharmaceutical add-on to facilitate the withdrawal process. Some drugs seem to be associated with beneficial effects, but the quality of the evidence was too low to lead to any clinical recommendations.

Implications for research

Future research of the potential of pharmacological agents to facilitate benzodiazepine withdrawal should focus on drugs with a potential to benefit the patients according to the results of the current meta-analysis and limit the different pharmacological interventions evaluated. Such randomised controlled trials should be assessed versus adequate placebo or nocebo to provide proper blinding and be designed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (Chan 2015), and reported according to the CONSORT guidelines (Schulz 2011).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Ashton 1990

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Blinding:** Double **Duration:** 12 weeks Single-centre
Participants	**Baseline characteristics** Buspirone • Years of benzodiazepine use, mean (SD): 9.5 (5.6) • Male, N (%): 3 (27.3) • Age, mean (SD): 39.8 (10.2) • Benzodiazepine dose (mg diazepam equivalents), mean (SD): 15.5 (8.2) Placebo • Years of benzodiazepine use, mean (SD): 11.25 (4.47)

Ashton 1990 *(Continued)*

- Male, N (%): 6 (50.0)
- Age, mean (SD): 43.4 (10.9)
- Benzodiazepine dose (mg diazepam equivalents), mean (SD): 7.5 (4.6)

Inclusion criteria: above 18 years of age, continuous benzodiazepine therapy for a minimum of 6 months, wish to withdraw from benzodiazepines

Exclusion criteria: use of other psychotropic medication, abuse of alcohol or drugs, major psychiatric or physical disease

Pretreatment group differences: Mean benzodiazepine dosage at baseline was 15.5 mg in buspirone group and 7.5 mg in placebo group.

Interventions	Benzodiazepine taper schedule: all participants switched to an equivalent dose of diazepam, stable dosage for 4 weeks, then taper with 25% each week for 4 weeks to 0, then 4 weeks without benzodiazepines. 1. Benzodiazepine taper schedule + buspirone 5 mg 3 times a day (N = 11). 2. Benzodiazepine taper schedule + placebo (N = 12).
Outcomes	• Benzodiazepine withdrawal symptoms: Ashton scale • Benzodiazepine cessation • Relapse to benzodiazepine use • Anxiety: Hospital Anxiety Depression Scale
Identification	**Sponsorship source:** Bristol Myers CNS provided buspirone and placebo tablets and covered laboratory and administrative expenses. **Country:** UK **Setting:** Outpatients, participants referred from their GP, rapid benzodiazepine tapering regimen **Declarations of interest:** Not mentioned **Author's name:** Ashton CH **Institution:** Department of Pharmacological Sciences, University of Newcastle upon Tyne, NE2 4HH **Email:** **Address:** Department of Pharmacological Sciences, University of Newcastle upon Tyne, NE2 4HH
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly assigned..." Comment: Not further described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: The study was carried out double-blind using matching placebo tablets. Quote: "double-blind...either buspirone or matching placebo tablets..."

Ashton 1990 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: No actions to adjust for high dropout (64%) in the intervention group compared with the placebo group (8%).
Selective reporting (reporting bias)	Low risk	Comment: No protocol available, but no reason to suspect selective outcome reporting
Other bias	Unclear risk	Comment: The role of Bristol Myers insufficiently described.

Baandrup 2016

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Blinding:** Double **Duration:** 24 weeks Single-centre
Participants	**Baseline characteristics** Pronlonged-release melatonin (PRM) • Years of benzodiazepine use, mean (SD): 10.4 (7.7) • Male, N (%): 23 (55) • Age, mean (SD): 47.9 (8.7) • Benzodiazepine dose (mg diazepam equivalents), mean (SD): 24.5 (20.1) Placebo • Years of benzodiazepine use, mean (SD): 10.5 (6.8) • Male, N (%): 25 (57) • Age, mean (SD): 49.4 (12.3) • Benzodiazepine dose (mg diazepam equivalents), mean (SD): 23.1 (14.1) **Inclusion criteria:** Age 18 years or above, an ICD-10 diagnosis of schizophrenia (F20), schizoaffective disorder (F25), or bipolar disorder (F31). Bipolar patients were required to be euthymic a the time of inclusion. Treatment with antipsychotic drug(s) for at least 3 months before inclusion, treatment with 1 or more benzodiazepine derivatives or benzodiazepine-related drugs for at least 3 months before inclusion, fertile women: negative pregnancy test at baseline and the use of safe contraceptives (intrauterine devices or hormonal contraception) throughout the trial period, written informed consent. **Exclusion criteria:** Known aggressive or violent behaviour, mental retardation, pervasive developmental disorder, or dementia, epilepsy, terminal illness, severe somatic comorbidity, or inability to understand Danish, allergy to compounds in the trial medication (melatonin, lactose, starch, gelatine, and talc), hepatic impairment, pregnancy or nursing, lack of informed consent. **Pretreatment group differences:** None
Interventions	Benzodiazepine taper schedule: gradual reduction of usual benzodiazepine dosage (including benzodiazepine-related drugs) at an approximate rate of 10% to 20% every second week.

Baandrup 2016 *(Continued)*

1. Benzodiazepine taper schedule + PRM 2 mg x 1 (N = 42).
2. Benzodiazepine taper schedule + placebo (N = 44).

Outcomes	• Benzodiazepine cessation • Benzodiazepine mean dose • SAEs • Non-serious AEs • Discontinuation due to AEs • Subjective sleep quality
Identification	**Sponsorship source:** The Research Fund of the Mental Health Services of the Capital Region in Denmark financed the trial with a post doc grant and a grant for external randomisation and database management. **Country:** Denmark **Setting:** Mainly outpatients **Declarations of interest:** None **Author's name:** Baandrup L **Institution:** Centre for Neuropsychiatric Schizophrenia Research (CNSR) & Centre for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS), University of Copenhagen, Mental Health Centre Glostrup, Mental Health Services – Capital Region of Denmark, Glostrup **Email:** lone.baandrup@regionh.dk **Address:** Mental Health Centre Glostrup, Mental Health Services – Capital Region of Denmark, DK-2600 Glostrup
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Central randomisation was performed by the Copenhagen Trial Unit (CTU) with computer-generated, permuted randomisation allocation sequence"
Allocation concealment (selection bias)	Low risk	Quote: "The allocation sequence and block sizes were kept unknown to the investigator. Allocation ratio was 1:1. The investigator contacted the CTU and provided a personal pin code, participant civil registration number, participant trial identification number, and the value of the stratification variable of benzodiazepine dosage (low (15 mg diazepam equivalents) or high (15 mg diazepam equivalents)) at baseline. Then the randomisation was announced as a trial medication container number and confirmation sent by e-mail"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Thus, the placebo was matched to the study medication for taste, smell, colour, size and solubility. CTU held the randomisation code and the trial was not unblinded until all data were registered, primary analyses finished and conclusions drawn"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Trial participants, staff, and outcome assessors were blinded to the allocated treatment. We maintained blinding using matching placebo and an independent unit to perform the randomisation and do the packaging and labelling of the trial medication. Both PRM and placebo were encapsulated in lactose- containing gelatine capsules to optimise the blinding"

Baandrup 2016 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Data complete for the primary outcome.
Selective reporting (reporting bias)	Low risk	Comment: Primary outcome, etc. reported in published trial protocol.
Other bias	Low risk	Comment: No other apparent source of bias

Cassano 1996

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Blinding:** Double **Duration:** 6 weeks (4 weeks double-blind followed by 2 weeks single-blind placebo) Multicentre
Participants	**Baseline characteristics** Alpidem • Male, N (%): 33 (37.9) • Age, mean (SD): 45.5 (11.3) • Years of benzodiazepine use, mean (SD): 4.7 Placebo • Male, N (%): 29 (33.7) • Age, mean (SD): 43.9 (11.4) • Years of benzodiazepine use, mean (SD): 5.1 **Inclusion criteria:** Outpatients with generalised anxiety disorder (GAD; DSM-III-R, item 300.02) or adjustment disorder with anxious mood (DSM-III-R, item 309.24). Consecutive patients of either sexes, aged between 18 and 60 years, taking non-hypnotic benzodiazepines for anxiety as continuous course of therapy of at least 1 year duration, at a dose schedule corresponding to 30 mg or less of diazepam per day, were considered eligible. **Exclusion criteria:** Montgomery–Åsberg Depression Rating Scale was administered to exclude depressed patients (total score > 18). **Pretreatment:** No significant differences
Interventions	**Intervention characteristics** Benzodiazepine taper schedule: all benzodiazepines abruptly discontinued at inclusion. 1. Benzodiazepine taper schedule + alpidem 100 to 150 mg/d(N = 87). 2. Benzodiazepine taper schedule + placebo(N = 86).
Outcomes	• Anxiety: HAM-A • Non-serious adverse events • Withdrawal syndrome (clinical diagnosis)
Identification	**Sponsorship source:** No information

Cassano 1996 *(Continued)*

	Country: Italy **Setting:** Outpatients **Declarations of interest:** Not mentioned **Author's name:** Cassano GB **Institution:** Clinica Psichiatrica, University degli Studi di Pisa **Email:** **Address:** Clinica Psichiatrica, University degli Studi di Pisa, Ospedale Santa Chiara, Via Roma 67, 56100 Pisa
Notes	The study lasted 6 weeks: a 4-week comparative period (phase I) to prevent and treat benzodiazepine withdrawal symptoms (primary aim) was followed by a 2-week single-blind period with placebo (phase II) to monitor the occurrence of withdrawal symptoms after abrupt discontinuation of alpidem (secondary aim). 6 weeks was chosen as endpoint because alpidem is a Z-drug. According to the review protocol, such studies are included if data are available on relevant outcomes AFTER withdrawal of the new benzodiazepine/Z-drug, in this case after discontinuation of alpidem.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Not described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The Italian multicentre (15 centres), double-blind, randomised (versus placebo), parallel group study" Comment: What has been done to ensure blinding of participants and study personnel is not described.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The diagnosis of withdrawal symptoms was made by a respected academic expert, in blind conditions, on the basis of the definition in the protocol" Comment: Done
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 10 (11.5%) discontinued in the alpidem group, 18 (21%) in the placebo group.
Selective reporting (reporting bias)	Low risk	Comment: Protocol published but could not be retrieved. No reason to suspect selective outcome reporting
Other bias	Unclear risk	Comment: Source of financing not described.

Cialdella 2001

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group

Cialdella 2001 *(Continued)*

	Blinding: Double **Duration:** 1 month Single-centre
Participants	**Baseline characteristics** Homéogène • Male, N (%): 4 (26.7) • Age, mean (SD): 52.9 (12.8) • Employed, N (%): 8 (53.3) • Benzodiazepine dose (diazepam equivalent), mean (SD): 4.5 (6.5) Sédatif PC • Male, N (%): 4 (20.0) • Age, mean (SD): 50.7 (11.9) • Employed, N (%): 8 (40.0) • Benzodiazepine dose (diazepam equivalent), mean (SD): 4.2 (4.7) Placebo • Male, N (%): 11 (42.3) • Age, mean (SD): 58.2 (15.3) • Employed, N (%): 7 (26.9) • Benzodiazepine dose (diazepam equivalent), mean (SD): 2.4 (2.6) **Inclusion criteria:** At least 18 years of age, at least 3 months use of benzodiazepines at low dosage (max 10 mg/day diazepam equivalents), clinically stable for at least 1 month **Exclusion criteria:** Severe insomnia, severe psychiatric disorders, alcohol or substance abuse disorder, previous seizures, current use of muscle relaxants, clonidine, or psychotropic drugs. **Pretreatment:** Higher scores on somatic symptoms in Homéogène group
Interventions	Benzodiazepines substituted (no taper schedule) with study drug: 1. Homéogène 6 tablets/day(N = 15) 2. Sédatif PC 6 tablets/day(N = 20) 3. placebo(N = 26) Both experimental drugs were homeopathic drugs.
Outcomes	• Benzodiazepine cessation • Hamilton Anxiety Rating Scale (HAM-A) • Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ)
Identification	**Sponsorship source:** Laboratoires Boiron, l'Agence Nationale de Valirisation de la Recherce **Country:** France **Setting:** Outpatients **Declarations of interest:** Not mentioned **Author's name:** Cialdella P **Institution:** Service de Pharmacologie Clinique, Faculté RTH Laënnec **Email:**

Cialdella 2001 *(Continued)*

	Address:
Notes	Homéogène and Sédatif groups were combined as 1 homeopathic drug group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Not described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: Described as double-blind, but lacks a description of what have been done to ensure blinding of participants and study personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Not described. Insufficient information to permit judgement of low or high risk of bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: 25% attrition. An ITT approach was used, but distribution of attrition between groups was not reported.
Selective reporting (reporting bias)	Low risk	Comment: No obvious selective outcome reporting
Other bias	Unclear risk	Comment: Role of funding source not described, both industry and publicly funded.

Di Costanzo 1992

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Blinding:** Double **Duration:** 4 weeks Single-centre
Participants	**Baseline characteristics** Carbamazepine • Benzodiazepine dose (diazepam equivalent), mean (SD): 18.7 (7.9) Placebo • Benzodiazepine dose (diazepam equivalent), mean (SD): 19.4 (9.5) **Inclusion criteria:** > 60 years of age, GAD, benzodiazepine abuse, minimum duration of benzodiazepine treatment 6 months **Exclusion criteria:** None described.

Di Costanzo 1992 *(Continued)*

	Pretreatment: No significant pretreatment differences
Interventions	Benzodiazepine taper schedule: 25% benzodiazepine dose reduction every week 1. Benzodiazepine taper schedule + carbamazepine dose adjusted to serum level 6 to 8 mcg/mL(N = 15) 2. Benzodiazepine taper schedule + placebo(N = 14)
Outcomes	• Benzodiazepine withdrawal symptoms: Physician Withdrawal Checklist • Benzodiazepine cessation • Discontinuation due to adverse events • Anxiety: HAM-A • Relapse to benzodiazepine use • Serious adverse events • Non-serious adverse events
Identification	**Sponsorship source:** Not reported **Country:** Italy **Setting:** Outpatients **Declarations of interest:** Not mentioned **Author's name:** Di Constanzo E **Institution:** Servizio Psichiatrico **Email:** **Address:** Viale Spellanzon, 55 31015 Conegliano
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Not described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: Described as double-blind, but what has been done to ensure blinding of participants and study personnel is not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Insufficient information to permit judgement of low or high risk
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 4 (26.6%) and 3 (21.4%) participants did not complete benzodiazepine cessation but participated in the study.
Selective reporting (reporting bias)	Low risk	Comment: No indication of selective outcome reporting

Di Costanzo 1992 *(Continued)*

Other bias	Low risk	Comment: No apparent other source of bias

Garfinkel 1999

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Blinding:** Double **Duration:** 6 weeks double-blind, 6 weeks single-blind Single-centre
Participants	**Baseline characteristics** Controlled-release melatonin • Male, N (%): 4 (22) • Age, mean (SD): 69 (11) • Number of benzodiazepine tablets, mean (SD): 1.08 (0.38) Placebo • Male, N (%): 5 (31) • Age, mean (SD): 68 (16) • Number of benzodiazepine tablets, mean (SD): 1.23 (0.61) **Inclusion criteria:** People with a daily use of benzodiazepines for more than 6 months, expressed willingness to discontinue the use, living independently **Exclusion criteria:** Cognitive impairment, liver or renal disorders **Pretreatment:** No significant differences
Interventions	**Intervention characteristics** Benzodiazepine taper schedule: participants were encouraged to reduce their usual benzodiazepine therapy dosage 50% during week 2, 75% during weeks 3 and 4, and then to discontinue benzodiazepine therapy completely during weeks 5 and 6. Participants who did not succeed in stopping benzodiazepine therapy during period 1 were encouraged to further reduce benzodiazepine dosage 50%, 75%, and 100% during weeks 8, 9 and 10, 11 and 12, respectively. 1. Benzodiazepine taper schedule + controlled-release melatonin 2 mg/d (2 hours before bedtime)(N = 18) 2. Benzodiazepine taper schedule + placebo(N = 16)
Outcomes	• Benzodiazepine cessation • Sleep quality (scale 1 to 10, higher = better)
Identification	**Sponsorship source:** Neurim Pharmaceuticals sponsored study medication and study nurse; statistical evaluations performed independently. **Country:** Israel **Setting:** Outpatients, living independently **Declarations of interest:** Not mentioned **Authors name:** Doron Garfinkel

Garfinkel 1999 *(Continued)*

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Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Not described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Subjects were randomised to receive either 2 mg of CRM therapy or a placebo that was identical in appearance"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Collection and entry of all data were completed before revealing the randomisation codes of the study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All included participants analysed.
Selective reporting (reporting bias)	Low risk	Comment: No indications of selective reporting
Other bias	High risk	Comment: The trial was partly financed by a company with an interest in given result, the company's role in interpreting the data is not sufficiently described.

Gerra 1993

Methods

Study design: Randomised controlled trial

Study grouping: Parallel group, stratifies for flunitrazepam/lormetazepam at baseline

Blinding: Single

Duration: 7 days

Single-centre

Participants

Baseline characteristics

Not reported

Inclusion criteria: 18 to 40 years of age, flunitrazepam abuse at a dose of 10 to 12 mg/day (18 participants) or lormetazepam abuse at a dose of 8 to 10 mg/day (18 participants). All participants met the criteria of the DSM-III-R for benzodiazepine withdrawal syndrome. Abuse was defined as use for at least 9 months. Informed consent was obtained from all participants.

Gerra 1993 *(Continued)*

	Excluded criteria: Psychiatric patients were not included in the study. Daily urine samples were taken to rule out the abuse of morphine, methadone, cocaine, amphetamine, barbiturates, cannabis, and ethanol during the study. **Pretreatment:** Not reported
Interventions	**Intervention characteristics** Benzodiazepine taper schedule: abrupt cessation 1. Benzodiazepine taper schedule + flumazenil 0.5 mg IV x 4/d days 1 to 4 and 0.5 mg x 2/d days 5 to 7. N = 18 (9 flunitrazepam abusers and 9 lormetazepam abusers) 2. Benzodiazepine taper schedule + placebo (saline solution). N = 18 (9 flunitrazepam abusers and 9 lormetazepam abusers)
Outcomes	• Serious adverse events • Non-serious adverse events • Anxiety, HAM-D • Benzodiazepine withdrawal symptoms (score 0 to 45) • Discontinuation due to adverse events • Benzodiazepine cessation
Identification	**Sponsorship source:** Not reported **Country:** Italy **Setting:** Inpatients **Declarations of interest:** Not mentioned **Author's name:** Gilberto Gerra **Institution:** University of Parma **Email:** **Address:** USL n. 4, Via Guasti S. Cecilia, 3, Parma 43100, Italy
Notes	Results were reported separately for flunitrazepam and lormetazepam users. To avoid including several comparisons from the same study, we only included results for the lormetazepam users in this meta-analysis (flunitrazepam is now very seldom used in clinical practice and in many countries is no longer registered for use).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Insufficient information
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Placebo groups B and D were only treated with saline solution for 7 days." Comment: Only participants were blinded.
Blinding of outcome assessment (detection bias)	High risk	Comment: Study only described as single-blinded, therefore probably not done.

Gerra 1993 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All participants analysed.
Selective reporting (reporting bias)	Low risk	Comment: No indication of selective outcome reporting
Other bias	Unclear risk	Comment: Insufficient information regarding sponsorship

Gerra 2002

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Blinding:** Single **Duration:** 8 days Single-centre
Participants	**Baseline characteristics** Flumazenil IV • Male, N (%): 9 (45) • Age, mean (SD): 35.9 Oxazepam tapering • Male, N (%): 11 (55) • Age, mean (SD): 38.2 Placebo • Male, N (%): 6 (60) • Age, mean (SD): 35.4 **Inclusion criteria:** History of benzodiazepine dependence according to DSM-IV criteria. **Exclusion criteria:** Severe chronic liver or renal diseases or other chronic physical disorders, recent onset of significant weight loss or gain, endocrinopathies, neurological disorders, immunopathy, in particular HIV disease, a positive family history of cardiovascular disease and hypertension, current abuse of illicit drugs and alcohol **Pretreatment:** None in reported parameters
Interventions	**Intervention characteristics** All participants received high doses of oxazepam (120 mg/day) during the last week before detoxification (pretreatment week). 1. Benzodiazepine cessation + flumazenil 1.0 mg x 2 IV (N = 20) 2. Oxazepam tapering + placebo (saline solution IV)(N = 20) 3. Placebo + placebo(N = 10)
Outcomes	• Benzodiazepine withdrawal symptoms: self reported withdrawal scores

Gerra 2002 *(Continued)*

- Relapse to benzodiazepine use

Identification	**Sponsorship source:** Not mentioned **Country:** Italy **Setting:** Inpatients **Declarations of interest:** Not mentioned **Author's name:** Gilberto Gerra **Institution:** Addiction Research Center, Ser.T., AUSL, Parma, Italy **Email:** gerra@polaris.it **Address:** Gilberto Gerra, Centro Studi Farmacotossicodipendenze, Ser.T., A.U.S.L., Via Spalato 2,43100 Parma, Italy
Notes	Only the comparison between flumazenil and placebo was considered relevant and included in the meta-analysis, cf. *Cochrane Handbook* on multiple comparisons. Rate of relapse NOT reported for the placebo group because: (quote) Long-term outcome of group C (placebo) patients was not evaluated in comparison with A and B patients because they received low-dose benzodiazepine treatment for 2 weeks, immediately after the detoxification procedure, for ethical reasons.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Not described Quote: "The study was single-blind, randomised and placebo-controlled."
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "the trial was single-blind, permitting direct clinical interventions in the case of dramatic withdrawal symptoms"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: Not done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Though not clearly described, judging from the text it appears that no participants withdrew during the 8-day intervention trial.
Selective reporting (reporting bias)	Low risk	Comment: No reason to suspect selective outcome reporting
Other bias	Unclear risk	Comment: Funding not described.

GlaxoSmithKline 2002

Methods	**Study design:** Randomised controlled trial

GlaxoSmithKline 2002 *(Continued)*

Study grouping: Parallel group

Blinding: Double

Duration: 12 weeks

Multicentre

Participants	**Baseline characteristics** Paroxetine • Male, N (%): 10 (33) • Age, mean (SD): 51.8 (17.6) Placebo • Male, N (%): 11 (46) • Age, mean (SD): 46.3 (17.9) **Inclusion criteria:** Participants were males or females aged > 18 years suffering from 1 or more of the following anxiety disorders of non-severe degree in axis I: panic attack disorder (with or without agoraphobia), GAD, social anxiety/social phobia or mixed anxiety and depression disorder with significant anxiety; people continuously treated with benzodiazepines (any) for at least 6 consecutive months prior to the screening visit at doses between 2 and 8 mg/day of lorazepam or equivalent; a total score ≤ 16 on the HAM-A and MADRS at screening and baseline. **Exclusion criteria:** People suffering (or diagnosed within the 6 months prior to screening) from 1 or more of the following conditions: major depressive episode; post-traumatic stress disorder; obsessive-compulsive disorder; eating behavioural disorders, people diagnosed with dysthymia or who had suffered from dysthymia in the 6 months prior to screening; people with a concomitant psychotic disorder, or history of psychotic disorder; people having a concomitant bipolar disorder or history of bipolar disorder, or having a cyclothymic disorder, or had suffered from it in the past; people who met DSM-IV (protocol appendix O) criteria for substance (alcohol or drugs) abuse or dependence, except for benzodiazepine, within 6 months prior to screening; current suicidal or homicidal risk; and people who had electroconvulsive therapy in the 3 months prior to screening. **Pretreatment:** No significant group differences
Interventions	**Intervention characteristics** Benzodiazepine taper schedule: 4-week open-label run-in period during which participants were switched from their original benzodiazepine to an equivalent dosage of chlordemethyldiazepam (between 2 and 8 mg/d). The taper schedule during the treatment phase not described. 1. Benzodiazepine taper + paroxetine 10 mg/d for the first week, 10 to 20 mg/d during weeks 2 to 8, 20 mg/d during weeks 9 to 12(N = 30) 2. Benzodiazepine taper + placebo(N = 24)
Outcomes	• Serious adverse events • Anxiety: HAM-A • Non-serious adverse events • Relapse to benzodiazepine use • Benzodiazepine withdrawal symptoms: BWSQ • Benzodiazepine cessation
Identification	**Sponsorship source:** GlaxoSmithKline **Country:** Italy **Setting:** Outpatients

GlaxoSmithKline 2002 *(Continued)*

	Declarations of interest: Not mentioned **Comments:** Unpublished phase III study **Author's name:** GlaxoSmithKline **Institution:** **Email:** **Address:** Clinical Study Register (www.gskclinicalstudyregister.com) 2002
Notes	Change scores extracted, final scores not available. Standard deviation calculated from CI using the following formula: SE = (upper limit – lower limit of CI)/3.92 Standard deviation σ = standard error x √n

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "12-week double blind, multicentre, randomised, placebo-controlled, parallel group" Comment: Not described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Subjects were randomised to either paroxetine or placebo and entered the 12-week double-blind, randomised treatment phase. Dosage of paroxetine or matched placebo started with..." Comment: Double-blind and using matched placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 2 versus 8 participants withdrew, but ITT analysis data extracted for this meta-analysis.
Selective reporting (reporting bias)	High risk	Comment: No protocol available, benzodiazepine dose at follow-up not described.
Other bias	High risk	Comment: Study funded by the study drug manufacturer, no information available on involvement in design, data collection, etc.

Hadley 2012

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Blinding:** Double

Hadley 2012 *(Continued)*

	Duration: 12 weeks (6 weeks during tapering and 6 weeks post-tapering) Multicentre
Participants	**Baseline characteristics** Pregabalin • Male, N (%): 14 (25) • Age, mean (SD): 40.1 (10.6) Placebo • Male, N (%): 16 (32) • Age, mean (SD): 43.5 (11.3) **Inclusion criteria:** Adult outpatients aged 18 to 65 years were enrolled if they met DSM-IV criteria for a primary lifetime diagnosis of GAD, and if they were receiving stable treatment with a benzodiazepine in daily doses of 1 to 4 mg/day (in alprazolam dose equivalents) for 8 to 52 weeks. A primary diagnosis of GAD was made, based on predominant clinical presentation, using the module P form of the Mini International Neuropsychiatric Interview (MINI)-Plus version 5.0.0 (Sheehan et al, 1997). The current diagnosis of GAD could be sub-threshold due to treatment. **Exclusion criteria:** (1) women who were pregnant, lactating, or of childbearing potential who were not using a medically approved form of contraception; (2) 17-item HAM-D total score > 15; (3) a history of anxiolytic non-response to benzodiazepines or pregabalin, or hypersensitivity to either class of drug; (4) they met DSM-IV criteria in the past 6 months of major depressive disorder, dysthymia, social phobia, post-traumatic stress disorder, body dysmorphic disorder, or eating disorder; (5) met DSM-IV criteria in the past 5 years of schizophrenia, psychotic disorder, bipolar affective disorder, obsessive–compulsive disorder, substance dependence (excluding nicotine), or in the past year for substance abuse; (6) currently receiving cognitive behavioural therapy for GAD or other anxiety disorder; (7) a history of seizure disorder, except febrile seizures of childhood; (8) a history of neuropathic pain or narrow angle glaucoma; (9) receiving treatment with fluoxetine (in past 5 weeks) or any psychotropic other than benzodiazepines (in past 2 weeks), or electroconvulsive therapy (in past 6 months); (10) positive urine drug screen for amphetamines, barbiturates, ethanol, narcotics, non-benzodiazepine sedatives and hypnotics, cocaine, phencyclidine, cannabinoids or other illegal or illicit drugs; (11) considered by the investigator to be at risk for suicide or aggressive behaviour; (12) any serious or uncontrolled medical illness in the opinion of the investigator that would render the person unsuitable for the study; or (13) creatinine clearance 60 mL/min. **Pretreatment:** None
Interventions	**Intervention characteristics** Benzodiazepine taper schedule: switch to equivalent dose alprazolam, 2-week stabilisation phase before randomisation, 25% reduction per week, permitted up to 6 weeks to complete the alprazolam taper, after maintained 6 weeks on double-blind treatment, then 1 week taper off study medication 1. Benzodiazepine taper schedule + pregabalin 150 to 600 mg/d according to tolerability and efficacy(N = 56). 2. Benzodiazepine taper schedule + placebo(N = 50).
Outcomes	• Benzodiazepine cessation • Anxiety, HAM-A • Non-serious adverse events • Serious adverse events • Benzodiazepine withdrawal symptoms, PWC
Identification	**Sponsorship source:** Funded by Pfizer

Hadley 2012 *(Continued)*

Country: 20 investigational sites in Spain, Mexico, France, Italy, Costa Rica, the Czech Republic, and Guatemala

Setting: Outpatients

Declarations of interest: Dr Schweizer was at the time of the writing of the manuscript employee of Paladin Consulting Group Inc., which was a paid consultancy to Pfizer Inc. At the time the study was conducted and the paper was initially drafted, Dr Sallie J Hadley was an employee of Pfizer Inc. and owns stock in Pfizer. Dr Francine S Mandel was a full-time employee of Pfizer Inc. Dr Edward Schweizer owns stock in Pfizer and has received payments for consulting and/or medical writing services from Alkermes, Bristol-Myers Squibb, Sumitomo Dainippon Pharma, Eli Lilly, Memory Pharmaceuticals, Neurocrine Biosciences, and Pfizer Inc.

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Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Not described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Patients...were randomised on a one-to-one basis to 12 weeks of double-blind treatment with either pregabalin or placebo" Comment: Described as "double-blind" but what has been done to ensure blinding of participants and study personnel is not mentioned.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: High attrition rate in both the pregabalin group (46.4%) and the placebo group (62.0%)
Selective reporting (reporting bias)	Low risk	Comment: No apparent selective outcome reporting
Other bias	High risk	Comment: Study funded by Pfizer, no indication of role of funding body in design, data collection, analysis, and interpretation of the data.

Hantouche 1998

Methods

Study design: Randomised controlled trial

Study grouping: Parallel group

Hantouche 1998 *(Continued)*

	Blinding: Double **Duration:** 3 months Multicentre
Participants	**Baseline characteristics** Magnesium aspartate • Male, N (%): 17 (29) • Age, mean (SD): 44.1 (10.8) • Employed, N (%): 45 (77) Placebo • Male, N (%): 20 (27) • Age, mean (SD): 44.7 (12.1) • Employed, N (%): 55 (73) **Inclusion criteria:** Outpatients, 18 to 65 years of age, chronic users of lorazepam, alprazolam, or bromazepam (> 6 months, regular dose => 3 mg lorazepam equivalents), benzodiazepines prescribed due to an anxious disorder now in remission defined as score on Hamilton Anxiety < 14 and Raskin-Depression < 6, no major psychiatric disorder, at least 1 trial of unsuccessful benzodiazepine withdrawal, a wish to discontinue benzodiazepine use **Exclusion criteria:** Severe hepatic or renal dysfunction, alcohol or substance use disorder, currently trying to discontinue use of tobacco, current psychotherapy, use of other psychotropics within 6 months, treatment with a magnesium salt or calcium within 1 month, regular use of magnesium aspartate during 1 month within the last 6 months **Pretreatment:** No significant pretreatment group differences
Interventions	Benzodiazepine taper schedule: co-administration of benzodiazepine and study drug for 1 month, gradual taper of benzodiazepine during the next month (50% of dosage for 2 weeks, 25% for 2 weeks, then stop), follow-up during a third month after complete benzodiazepine discontinuation 1. Benzodiazepine taper schedule + magnesium aspartate 2 capsules x 3 (300 mg magnesium/day)(N = 69) 2. Benzodiazepine taper schedule + placebo(N = 75)
Outcomes	• Benzodiazepine cessation • Anxiety • Non-serious AEs • Relapse to benzodiazepine use • Discontinuation due to AEs
Identification	**Sponsorship source:** Not reported **Country:** France **Setting:** Outpatients **Declarations of interest:** Not mentioned **Author's name:** Hantouche EG **Institution:** Département de Psychiatrie, Groupe Hospitaliers de la Pitrie-Salpetriere **Email:** **Address:** 47, Boulevard de l'Hopital, 75013 Paris

Hantouche 1998 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Not described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: Described as double-blind, what has been done to ensure blinding of participants and study personnel is not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: Not described
Selective reporting (reporting bias)	Low risk	Comment: No indications of reporting bias
Other bias	Low risk	Comment: No apparent other sources of bias

Harrison-Read 1996

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Blinding:** Double **Duration:** 3 weeks Single-centre
Participants	**Baseline characteristics** Flumazenil IV challenge • Male, N (%): 1 (25) • Age, mean (SD): 46 • Years of benzodiazepine use, mean (SD): 8.25 Placebo • Male, N (%): 2 (33) • Age, mean (SD): 42.3 • Years of benzodiazepine use, mean (SD): 8.5

Harrison-Read 1996 *(Continued)*

	Inclusion criteria: People were recruited to the study if they had been taking benzodiazepines in usual therapeutic doses (< 30 mg per day of diazepam or equivalent) for 3 months or more, and if they had experienced withdrawal problems on discontinuing medication. **Exclusion criteria:** (i) regular intake of any other psychotropic medication, (ii) a diagnosis of schizophrenia, epilepsy, or cardiorespiratory disease **Pretreatment:** No significant pretreatment differences
Interventions	**Intervention characteristics** 1. Flumazenil IV challenge 1 mg injected over 30 s, followed by an individually tailored phased withdrawal schedule which, if followed correctly, would produce complete abstinence (100% dose reduction) after 3 weeks following the challenge test(N = 4) 2. Placebo (vehicle solution alone) followed by identical benzodiazepine taper schedule(N = 6)
Outcomes	• Benzodiazepine dose reduction of 70% • Serious adverse events • Benzodiazepine mean dose • Benzodiazepine withdrawal symptoms: BWSQ • Non-serious adverse events
Identification	**Sponsorship source:** Roche Products Ltd supplied unmarked ampoules of flumazenil and vehicle solution and a grant towards the cost of the project. **Country:** UK **Setting:** Outpatients (inpatients when receiving flumazenil challenge) **Declarations of interest:** Not mentioned **Comments:** The study was approved by the local ethics committee but, owing to the unexpectedly severe reactions shown in some participants, it was felt to be unethical to continue with the study after 10 participants had been tested using the original protocol. **Author's name:** Harrison-Read PE **Institution:** Academic Unit of Psychiatry, St Charles Hospital, Exmoor Street, London W10 6DZ **Email:** **Address:** Academic Unit of Psychiatry, St Charles Hospital, Exmoor Street, London W10 6DZ
Notes	Study discontinued due to unacceptable adverse effects (marked panic reaction in the 4 participants who received flumazenil), beginning within 30 seconds of the end of the injection.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "High risk and low risk subjects were allocated separately at random to placebo or flumazenil challenge by an independent pharmacist." Comment: Description of how the sequence was generated was insufficient.
Allocation concealment (selection bias)	Low risk	Comment: Allocation was done by independent pharmacist.
Blinding of participants and personnel (performance bias)	Low risk	Quote: "This 'challenge test' was carried out double-blind, with both subject and experimenter being unaware of the identify of the substance being injected"

Harrison-Read 1996 *(Continued)*

All outcomes		Comment: Described as double-blind and using placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Immediately afterwards, the subject began filling in the BWSQ and the MRS, and then repeated these measures at 5, 15, 25, 35, 45 and 60 min post-injection. Pulse and blood pressure were recorded as before" Comment: Description is insufficient to judge the risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants analysed.
Selective reporting (reporting bias)	Low risk	Comment: No reason to suspect selective outcome reporting
Other bias	High risk	Comment: As the reaction to acute challenge with flumazenil proved to be unexpectedly severe, the study was stopped after only 10 participants had been recruited for the study: 4 were allocated to the flumazenil group and 6 to the placebo group. Despite separately randomising high- and low-risk participants, the early cessation of the study led to unequal distribution between the 2 treatment groups: 1 out of the 4 participants in the flumazenil group and 3 out of the 6 in the placebo group were high-risk participants. In addition, the study was supported by a company.

Klein 1994

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Blinding:** Double **Duration:** Approximately 5 weeks (dependent on duration of taper phase) Single-centre
Participants	**Baseline characteristics** Carbamazepine: not available Placebo: not available **Inclusion criteria:** DSM-III-R diagnosis of panic disorder or generalised anxiety disorder **Exclusion criteria:** 1) Lifetime history of psychotic disorder, 2) Bipolar disorder, 3) Seizure disorder, 4) Severe head trauma, 5) Major depression, 6) Abuse of alcohol or other substances, 7) Obsessive-compulsive disorder, 8) PTSD, 9) Pregnancy, 10) Active systemic illness with chronic medication **Pretreatment:** Reported to be non-significant but not reported for the carbamazepine versus placebo group, only reported for the panic disorder versus the GAD group
Interventions	**Intervention characteristics** Benzodiazepine taper schedule: 25% every third day 1. Benzodiazepine taper schedule + carbamazepine 400 to 800 mg/d(N = 38) 2. Benzodiazepine taper schedule + placebo(N = 34)
Outcomes	• Benzodiazepine mean dose

Klein 1994 *(Continued)*

- Benzodiazepine cessation

Identification	**Sponsorship source:** Supported by the Upjohn Company **Country:** Israel **Setting:** Outpatients **Declarations of interest:** Not mentioned **Author's name:** Ehud Klein **Institution:** Rambam Medical Center and University of Vermont **Email:** **Address:** Rambam Medical Center, Rapapport Faculty of Medicine, Technion-IIT, Bat Galim, Haifa, Israel
Notes	Baseline characteristics for the carbamazepine versus placebo group were not reported, only for panic disorder group versus generalised anxiety disorder group. Same problem when reporting the results

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Not described in detail, but it is stated that randomisation was stratified by diagnosis and alprazolam daily dosage
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients entered the controlled portion of the study and were randomly assigned, in a double-blind fashion, to receive either carbamazepine or placebo as adjunctive treatment...In order to maintain blindness of the study throughout the taper period, patients received a fixed number of capsules with a gradually increasing proportion of identical placebo capsules substituting for the alprazolam" Comment: The use of carbamazepine versus placebo (the primary interest for the current review) was double-blinded with identical placebo. The alprazolam taper was single-blind, but these data are not considered here.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Not sufficiently described
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: Very high dropout rates (56% vs 71%), and no ITT analysis performed.
Selective reporting (reporting bias)	High risk	Comment: No reporting on benzodiazepine dosage or withdrawal symptoms
Other bias	High risk	Comment: Role of supporting company not described

Kornowski 2002

Methods	**Study design:** Randomised controlled trial

Kornowski 2002 *(Continued)*

	Study grouping: Parallel group **Blinding:** Double **Duration:** 28 days Single-centre
Participants	**Baseline characteristics** Carbamazepine • Age, mean (SD): 43.29 (6.24) • Years of benzodiazepine use, mean (SD): 7.63 (6.91) • Benzodiazepine dose (diazepam equivalent), median (range): 27.63 (20.1) Tianeptine • Age, mean (SD): 44.79 (5.18) • Years of benzodiazepine use, mean (SD): 7.06 (6.12) • Benzodiazepine dose (diazepam equivalent), median (range): 28.45 (28.4) **Inclusion criteria:** ICD-10 criteria for benzodiazepine dependence, 18 to 65 years of age **Exclusion criteria:** Previously treated with 1 or both of the experimental drugs, psychotic symptoms, not treated with other psychotropic drugs until 2 weeks before inclusion, pregnant or nursing, substance abuse, severe somatic illness **Pretreatment:** No significant pretreatment differences
Interventions	Benzodiazepines substituted with 1. Carbamazepine 600 mg/day(N = 24) 2. Tianeptine 37.5 mg/day(N = 24)
Outcomes	• Benzodiazepine cessation • Relapse to benzodiazepine use • Serious AEs
Identification	**Sponsorship source:** Not mentioned **Country:** Poland **Setting:** Inpatients **Declarations of interest:** Not mentioned **Comments:** No data reported for the outcomes, only overall results from statistical analyses. **Author's name:** Kornowski J **Institution:** Psychiatric Hospital in Starogard Gdansk **Email:** kornowski@dobrynet.pl **Address:** 83-200 Starogard Gdansk
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Kornowski 2002 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Comment: Not described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: Blinding not described, not possible to judge whether participants and personnel were blinded, also it is not stated if the study was open-label.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 4 (17%) dropped out in each group because they ingested benzodiazepines during the trial(detected by urine screen), but all participants were included in the statistical analyses.
Selective reporting (reporting bias)	Low risk	Comment: No apparent reporting bias
Other bias	Unclear risk	Comment: No apparent other sources of bias

Lader 1987

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Blinding:** Double **Duration:** 6 weeks Single-centre
Participants	**Baseline characteristics** Only reported for the total sample: men: 41.7%; age: 39.1 years; years of benzodiazepine use: 8.4 years **Inclusion criteria:** More than 6 months of benzodiazepine use, physically dependent, no requirements of further benzodiazepine treatment as deemed by mental state assessment **Exclusion criteria:** Abuse of alcohol or other drugs **Pretreatment:** Not described
Interventions	**Intervention characteristics** Benzodiazepine taper schedule: 2 weeks on unchanged dosage, 2 weeks on halved benzodiazepine dosage, 2 weeks with no benzodiazepines (followed by 2 weeks with placebo in both groups and 2 weeks with no study medication) 1. Benzodiazepine taper schedule + buspirone 10 to 30 mg/d(N = 13) 2. Benzodiazepine taper schedule + placebo(N = 11)
Outcomes	• Benzodiazepine withdrawal symptoms, Tranquilizer Withdrawal Rating Scale • Insomnia: Sleep rating scale

Lader 1987 *(Continued)*

- Anxiety: HAM-A
- Benzodiazepine cessation

Identification	**Sponsorship source:** Not mentioned **Country:** UK **Setting:** Outpatients **Declarations of interest:** Not mentioned **Authors name:** Malcolm Lader **Institution:** Institute of Psychiatry, University of London **Email:** **Address:** Institute of Psychiatry, University of London, De Crespigny Park, Denmark Hill, London, SE5 8AF England
Notes	For reasons that are unclear, results are reported at week 3, i.e. after the first week of benzodiazepine reduction to half. That is, results are not available for week 6, when benzodiazepines have been tapered off. Figure 2 shows the temporal pattern for Hamilton Anxiety Scale (i.e. all time points available graphically) but only for the successful completers (5 buspirone, 6 placebo).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Not described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "During the first two weeks of withdrawal (3 and 4), buspirone or placebo was substituted for the benzodiazepine in an initial dosage of 5 mg (one capsule) twice daily, followed by 10 mg (two capsules) twice daily...The study was conducted double-blind in that neither investigator nor patient knew whether placebo or buspirone was being administered during weeks 2 to 5"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: It is stated that "investigators" were blinded. Judged as done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Successful completers: no attrition bias
Selective reporting (reporting bias)	Unclear risk	Comment: No data on benzodiazepine dosage in the 2 groups, but the trial was designed to stop benzodiazepine use, and therefore dose reduction was not considered. However, the choice of using 3 weeks as primary time point does not seem justified.
Other bias	Low risk	Comment: No other apparent source of bias

Lader 1993

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Blinding:** Double **Duration:** 8 weeks Single-centre
Participants	**Baseline characteristics** Alpidem (a Z-drug) • Male, N (%): 4 (31) Placebo • Male, N (%): 4 (33) **Inclusion criteria:** Benzodiazepine use for more than 6 months, less than 30 mg/d diazepam equivalents, regarded as dependent (problems on previous attempts to lower the dosage), 18 to 65 years of age, within 20% of normal body weight **Exclusion criteria:** Major physical or psychiatric illness, drug abusers, women of child-bearing age unless on adequate contraception **Pretreatment:** Not described
Interventions	**Intervention characteristics** Benzodiazepine taper schedule: 2 weeks on unchanged dosage, 2 weeks on halved benzodiazepine dosage, 2 weeks with no benzodiazepines (followed by 2 weeks with halved dosage study medication and 2 weeks with no study medication) 1. Benzodiazepine taper schedule + alpidem (a Z-drug) 100 to 150 mg/d(N = 13) 2. Benzodiazepine taper schedule + placebo(N = 12)
Outcomes	• Benzodiazepine cessation • Anxiety, HAM-A • Benzodiazepine withdrawal symptoms, Tranquilizer Withdrawal Rating Scale
Identification	**Sponsorship source:** Not described **Country:** UK **Setting:** Outpatients **Declarations of interest:** Not mentioned **Author's name:** Lader M **Institution:** Institute of Psychiatry **Email:** **Address:** Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SES 8AF, UK
Notes	Anxiety and benzodiazepine withdrawal symptoms: the results are only shown in graphic as mean values, SDs not reported. SDs for HAM-A were therefore imputed from Cassano 1996, which is a similar trial also using alpidem to facilitate benzodiazepine withdrawal. It was not possible to impute SDs for benzodiazepine withdrawal symptoms because withdrawal symptoms in Cassano 1996 were reported as a dichotomised variable, whereas they were reported as a continuous variable in Lader 1993.

Lader 1993 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Not described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The study was conducted double-blind in that neither investigators nor patients knew whether placebo or alpidem was being administered during weeks 3-8" Comment: Study described as double-blinded and using placebo.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: It is stated that "investigators" were blinded. Judged as done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: High dropout, however only completion could be extracted from the study, and this is not biased by the high dropout rate.
Selective reporting (reporting bias)	Low risk	Comment: No indications of selective reporting
Other bias	Low risk	Comment: No other apparent bias

Lecrubier 2005

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Blinding:** Double **Duration:** 16 weeks Multicentre
Participants	**Baseline characteristics** Lithium • Male, N (%): 46 (32) • Age, mean (SD): 49.3 (10.3) • Benzodiazepine dose (diazepam equivalent), mean (SD): 15.7 (7.0) Placebo • Male, N (%): 30 (31) • Age, mean (SD): 47.6 (11.2) • Benzodiazepine dose (diazepam equivalent), mean (SD): 13.5 (5.2) **Inclusion criteria:** Outpatients, 18 to 65 years old, receiving benzodiazepines for at least 6 months at a daily dose ranging from 10 to 40 mg diazepam or equivalent and wishing to withdraw benzodiazepine treatment

Lecrubier 2005 *(Continued)*

	Exclusion criteria: Anxiety disorder with a score of 15 or above on the HAM-A, major depressive disorder, social phobia, alcohol or substance abuse according to Mini International Neuropsychiatric Interview, and/or other serious pathology. Tranquilisers including antihistamines, hypnotics, anxiolytics, and lithium salts were not allowed. **Pretreatment:** No significant pretreatment group differences
Interventions	Benzodiazepine taper schedule: 4 weeks stable benzodiazepine and lithium versus placebo, 4 weeks benzodiazepine withdrawal - reduction with 50% every week, 8 weeks lithium maintenance 1. Benzodiazepine taper schedule + lithium 0.84 mg/day(N = 146) 2. Benzodiazepine taper schedule + placebo(N = 98)
Outcomes	• Benzodiazepine cessation • Serious AEs • Non-serious AEs • Discontinuation due to AEs
Identification	**Sponsorship source:** Not described **Country:** France **Setting:** Outpatients **Declarations of interest:** Not mentioned **Author's name:** Lecrubier **Institution:** Inserm unité 302, service de psychiatrie AD **Email:** lecru@ext.jussieu.fr **Address:** Hôpital Pitié-Salpêtrière, 17, boulevard de l'hôpital, 75013 Paris, France
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "double-blind, randomised study" Comment: Not sufficiently described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Lithium gluconate and placebo were dispensed in vials and were indistinguishable in terms of appearance, taste and smell"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Not sufficiently described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 244 participants were randomised: 146 to lithium and 98 to placebo. Only participants entering the benzodiazepine tapering phase were analysed (136 participants allocated to lithium and 94 to placebo), thus attrition rate of 7% and 4%, respectively.

Lecrubier 2005 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Comment: Benzodiazepine dose at endpoint not reported, only participants who succeeded in discontinuing benzodiazepine usage.
Other bias	Low risk	Comment: No other apparent source of bias

Lemoine 2006

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Blinding:** Double **Duration:** 4 weeks Multicentre
Participants	**Baseline characteristics** Bromazepam • Male, N (%): 20 (24) • Age, mean (SD): 48.2 (11.1) • Years of benzodiazepine use, mean (SD): 4.0 (5.6) • Months of benzodiazepine use, mean (SD): 47.4 (67.7) Cyamemazine • Male, N (%): 30 (39) • Age, mean (SD): 48.7 (10.2) • Years of benzodiazepine use, mean (SD): 4.5 (1.8) • Months of benzodiazepine use, mean (SD): 52.5 (21.4) **Inclusion criteria:** Participants were aged 18 to 65 years, treated for anxiety for at least 3 months with benzodiazepines (bromazepam, lorazepam, alprazolam, or oxazepam) at a daily dose of 5 to 20 mg diazepam-equivalent, and requiring a withdrawal. A < 18 score in the Hamilton Anxiety Rating Scale was required. **Exclusion criteria:** Female patients were excluded if they were pregnant or likely to become so or if they were breastfeeding. Individuals incapable of completing a questionnaire or of properly giving informed consent were also excluded. In addition, current treatment with any psychotropic drug or any other central nervous system active medication was forbidden. The presence of comorbid depression was also an exclusion criterion. **Pretreatment:** NS
Interventions	**Intervention characteristics** 1. Abrupt benzodiazepine cessation + bromazepam 3 to 6 mg/d(N = 83) 2. Abrupt benzodiazepine cessation + cyamemazine 25 to 50 mg/d(N = 77)
Outcomes	• Anxiety: maximum amplitude of rebound (HAM-A) • Non-serious adverse events • Relapse to benzodiazepine use • Discontinuation due to adverse events
Identification	**Sponsorship source:** Not described. 1 of the authors affiliated with Sanofi-Aventis.

Lemoine 2006 *(Continued)*

	Country: France
	Setting: Outpatients
	Declarations of interest: Not mentioned
	Author's name: Patrick Lemoine
	Institution: Unite´ Clinique de Psychiatrie Biologique, Bron
	Email: garayperso@aol.com
	Address: 46bis rue Gallie´ni, 91360 Villemoisson-sur-Orge, France
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Not described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both drugs were administered in identical soft gelatin capsules" Comment: Sufficient blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: ITT analysis performed.
Selective reporting (reporting bias)	High risk	Comment: Protocol not available, unusual primary outcome (maximum amplitude of anxiety rebound).
Other bias	High risk	Comment: Role of Sanofi-Aventis not described.

Mariani 2016

Methods	**Study design:** Randomised controlled trial
	Study grouping: Parallel group
	Blinding: Double
	Duration: 8 weeks
	Single-centre
Participants	**Baseline characteristics**
	Gabapentin

Mariani 2016 *(Continued)*

- Age, mean (SD): 40
- Male, N (%): 6 (75)

Placebo

- Age, mean (SD): 37
- Male, N (%): 8 (73)

Inclusion criteria: Meeting DSM-IV criteria for current benzodiazepine abuse or dependence and opioid dependence, and being treated for opioid dependence with methadone, 18 to 65 years of age

Exclusion criteria: (1) Any Axis I psychiatric disorder as defined by DSM-IV-TR that was unstable or would be disrupted by study medication or by an effort to discontinue benzodiazepines; (2) Acute physiological withdrawal or a history of seizures during alcohol or sedative-hypnotic withdrawal; (3) Individuals with cocaine dependence as their primary substance use disorder diagnosis; (4) Individuals with unstable physical disorders or impaired kidney function; (5) Prescribed psychotropic medications other than methadone or medications prescribed for pain syndromes that would be disrupted by study medication or by an effort to discontinue benzodiazepines; (6) Anticonvulsants prescribed for pain syndromes; (7) Known sensitivity to gabapentin; (8) Individuals who had exhibited suicidal or homicidal behaviour within the past 2 years or had current active suicidal ideation; (9) Individuals physiologically dependent on any other drugs (excluding nicotine, caffeine, methadone); (10) Individuals currently prescribed gabapentin; and (11) Individuals requiring pharmacological detoxification from benzodiazepines in the past year and are unlikely to be able to tolerate taper off of benzodiazepines

Pretreament differences: None reported.

Interventions	**Intervention characteristics** 1. Abrupt benzodiazepine cessation + gabapentin 1200 mg 3 times daily(N = 8) 2. Abrupt benzodiazepine cessation (control group)(N = 11)
Outcomes	Benzodiazepine mean dose
Identification	**Sponsorship source:** Funding for this work was provided by National Institute on Drug Abuse grants K23- DA021209 (Mariani), P50-DA09236 (Kleber), K24- DA022412 (Nunes), and K24 029647 (Levin). **Country:** USA **Setting:** Methadone maintenance outpatients **Declarations of interest:** None **Authors name:** John J Mariani **Institution:** Division on Substance Abuse, New York State Psychiatric Institute, New York, NY, USA **Email:** jm2330@columbia.edu **Address:** New York State Psychiatric Institute, Division on Substance Abuse, 1051 Riverside Drive, Unit 66, New York, NY 10032, USA
Notes	Data not reported sufficiently, not possible to extract results relevant to this review. The author has not responded to our queries.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Randomisation method not described.

Mariani 2016 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: All capsules were over-capsulated with riboflavin to ensure compliance.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: Only 50% were retained in the study.
Selective reporting (reporting bias)	Low risk	Comment: Selective outcome reporting not evident.
Other bias	Low risk	Comment: No other apparent source of bias

Mercier-Guyon 2004

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Blinding:** Double **Duration:** 6 weeks (2 weeks taper off, 4 weeks assessment, ends day 45) Multicentre
Participants	**Baseline characteristics** Captodiame • Age, mean (SD): 39.1 (1.3) • Male, N (%): 20 (50) Placebo • Age, mean (SD): 41.9 (1.4) • Male, N (%): 20 (48.8) **Inclusion criteria:** Participants aged 25 to 55 years who had been prescribed certain benzodiazepines (lorazepam, bromazepam, alprazolam, oxazepam, or clobazam) in the official recommended dose range for the treatment of an anxiety disorder for at least 6 months, stable benzodiazepine dosage over the 6-month period. Since alertness was assessed with a driving simulation test, included participants were required to be in possession of a valid driving license for at least 5 years. **Exclusion criteria:** People with a history of alcohol dependence in the previous 5 years were excluded, as were those consuming excessive quantities of alcohol as defined in the CAGE questionnaire. Proven consumption (either openly declared or detected by urine testing) of illicit psychotropic drugs (opiates, cocaine, cannabis, amphetamines) or of any other sedatives also constituted grounds for exclusion. Additionally, people with severe, unstable, or uncontrolled hepatic, renal, or cardiac insufficiency, with glaucoma or prostate hypertrophy, or with any psychiatric disease other than generalised anxiety disorders were also excluded. Female individuals who were pregnant or breastfeeding were excluded.

Mercier-Guyon 2004 *(Continued)*

	Pretreatment: No significant group differences
Interventions	**Intervention characteristics** Benzodiazepine taper schedule: half dose first week of experimental treatment, a quarter dose the second week, then discontinuation on day 14 1. Benzodiazepine taper schedule + captodiame 150 mg/d(N = 40) 2. Benzodiazepine taper schedule + placebo(N = 41)
Outcomes	• Benzodiazepine withdrawal symptoms, BWSQ • Non-serious adverse events • Anxiety, Hamilton Anxiety Rating Scale • Serious adverse events
Identification	**Sponsorship source:** This study was funded by Laboratoires Bailly-Creat, Paris, France, manufacturers of captodiame (Covatine), who financed the honoraria of the participating physicians and the statistical analysis. **Country:** France **Setting:** Outpatients **Declarations of interest:** Not mentioned **Comments:** Benzodiazepine dose during and after discontinuation not recorded/documented. **Authors name:** Merzecier-Guyon C **Institution:** Centre d'Etudes et de Recherches en Médecine du Trafic, Annecy, France **Email:** cermtcmg@wanadoo.fr **Address:** Dr C Mercier-Guyon, CERMT, BP 132, 74004 ANNECY Cedex, France
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Not sufficiently described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "randomised, double-blind, placebo-controlled trial" Comment: What has been done to ensure blinding of participants and study personnel is not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants analysed.

Mercier-Guyon 2004 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Quote: "we have little information available on real benzodiazepine use during the discontinuation and follow-up phases, which is the most relevant measure of successful benzodiazepine" Comment: No information due to study design, not interpreted as being left out intentionally
Other bias	High risk	Quote: "This study was funded by Laboratoires Bailly-Creat, Paris, France, manufacturers of captodiamine (Covatine), who financed the honoraria of the participating physicians and the statistical analysis." Comment: No indication of sponsor's influence on study analysis, etc.; interpreted as high risk of bias

Morton 1995

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Blinding:** Double **Duration:** 16 weeks Single-centre
Participants	**Baseline characteristics** Not described **Inclusion criteria:** Referred to Benzodiazepine Withdrawal Clinic, benzodiazepines had been taken long term (> 6 months) at normal dose (< 30 mg/day of diazepam or equivalent), 18 to 70 years of age, body weight within normal limits **Exclusion criteria:** Major physical or psychiatric illnesses, drug abuse, women of childbearing age unless taking effective contraceptive measures **Pretreatment:** Not reported
Interventions	**Intervention characteristics** Benzodiazepine taper schedule: 4 weeks buspirone/placebo stabilisation, 6 weeks tapering to zero, 4 weeks of benzodiazepine abstinence, buspirone/placebo halved in dosage and then stopped 2 weeks later 1. Benzodiazepine taper schedule + buspirone flexible dosing, min 15 mg/d, mean 25 mg/day (N = 12) 2. Benzodiazepine taper schedule + placebo(N = 12)
Outcomes	• Benzodiazepine cessation • Anxiety, HAM-A • Benzodiazepine withdrawal symptoms, benzodiazepine withdrawal profile • Non-serious adverse events
Identification	**Sponsorship source:** This study was supported by a grant from Bristol-Myers Squibb UK to the Institute of Psychiatry. **Country:** UK **Setting:** Outpatients

Morton 1995 *(Continued)*

	Declarations of interest: Not mentioned **Author's name:** Morton S **Institution:** Institute of Psychiatry, University of London **Email:** **Address:** Institute of Psychiatry, De Crespigny Park, London SE5 8AFUK
Notes	Means only given in figures (HAM-A and benzodiazepine withdrawal symptoms), no SDs reported, not possible to impute in a methodologically valid way.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Not described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Half the patients were given buspirone in flexible dosage according to the usual criteria of clinical need, at a minimum of 15 mg/day in divided doses. The others received matching placebo in equivalent flexible dosage, again according to apparent clinical need...The study was conducted double-blind with reference to whether buspirone or placebo was being administered in weeks 2-18" Comment: Done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: No risk of bias regarding the main outcome (benzodiazepine cessation), but the secondary outcomes were only analysed for the participants who had discontinued treatment, i.e. half of the participants.
Selective reporting (reporting bias)	Low risk	Comment: No reason to suspect selective outcome reporting
Other bias	High risk	Comment: Financed by a grant from Bristol-Myers Squibb, but further information on potential influence on design, etc. not provided.

Nakao 2006

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel **Blinding:** None, open-label **Duration:** 8 weeks Single-centre
Participants	**Baseline characteristics:** Not reported

Nakao 2006 *(Continued)*

	Inclusion criteria: The participant selection criteria were as follows: (i) those aged 20 to 70 years; (ii) those whose medical condition was stable and drug regimens unchanged for longer than 3 months; (iii) those who had been prescribed either alprazolam, bromazepam, etizolam, or lorazepam for at least 3 months prior to visiting the clinic; and (iv) those who were able to visit the clinic for an 8-week intervention (or control) period. **Exclusion criteria:** DSM-IV major depression **Pretreatment:** No baseline characteristics provided.
Interventions	**Intervention characteristics** Benzodiazepine taper schedule: 8-week gradual benzodiazepine discontinuation 1. Benzodiazepine taper schedule + paroxetine 10 to 20 mg(N = 22) 2. Benzodiazepine taper schedule (control group, no placebo)(N = 23)
Outcomes	• Anxiety, HAM-A • Benzodiazepine withdrawal symptoms, Benzodiazepine Withdrawal Symptom Questionnaire
Identification	**Sponsorship source:** Not described **Country:** Japan **Setting:** Outpatients **Declarations of interest:** Not mentioned **Author's name:** Nakao M **Institution:** Division of Psychosomatic Medicine, Teikyo University Hospital **Email:** mnakao@med.teikyo-u.ac.jp **Address:** Department of Hygiene and Public Health, Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi-ku, Tokyo, Japan
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Not described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: No placebo: open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: Not done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants analysed.

Nakao 2006 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: No protocol provided, but all relevant outcomes seem to be reported.
Other bias	Unclear risk	Comment: No other apparent biases, the funding of the study not described.

Pat-Horenczyk 1998

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Blinding:** Double **Duration:** 4 weeks Single-centre
Participants	**Baseline characteristics** Zopiclone • Age, mean (SD): 52.7 (6.05) Flunitrazepam • Age, mean (SD): 49 (10.6) **Inclusion criteria:** Long-term usage of benzodiazepine hypnotics (range 6 months to 22 years), use of flunitrazepam for at least 3 months with stabilisation at a nightly dosage of 1 mg for at least 1 month before inclusion **Exclusion criteria:** Other benzodiazepine consumption, use of psychotropic medications **Pretreatment:** No significant group differences
Interventions	**Intervention characteristics** Benzodiazepine taper schedule: during the first part of the study, participants were either switched gradually to 1) zopiclone (3.75 mg and then 7.5 mg) over a 2-week period (N = 7), or 2) continued their usual treatment of flunitrazepam 1 mg (N = 11). In the second part of the trial, the hypnotic (either zopiclone or flunitrazepam) was gradually withdrawn according to a 2-step scheme over 2 weeks.
Outcomes	• Benzodiazepine withdrawal symptoms, Ashton Withdrawal Symptom Checklist, the Benzodiazepine Withdrawal Scale, the Benzodiazepine Withdrawal Symptom Questionnaire • Relapse to benzodiazepine use • Insomnia: total sleep time (and a range of other polysomnographic measures)
Identification	**Sponsorship source:** This study was supported by Rhone-Poulenc Rorer Ltd, France, and the Technion Sleep Medicine Center, Israel **Country:** Israel **Setting:** Outpatients **Declarations of interest:** Not mentioned **Authors name:** Ruth Pat-Horenczyk

Pat-Horenczyk 1998 *(Continued)*

	Institution: Technion Sleep Laboratory, Faculty of Medicine **Email:** **Address:** Technion Sleep Laboratory, Faculty of Medicine, Gutwirth Building, Technion-Israel Institute of Technology, Haifa 32000, Israel
Notes	Data from the benzodiazepine withdrawal questionnaires were not reported, thus only data on benzodiazepine relapse and insomnia could be extracted from this trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Not described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind randomised", "ZOP and FLU were encapsulated, and dummy placebo capsules were given to the patients who did not switch to ZOP, so that during the 5-week period, all patients consumed", "two identical-looking pills each night." Comment: Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Not sufficiently described
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 20/24 participants completed the 5-week withdrawal programme, however analysis was performed on women only due to uneven gender distribution between groups and high dropout rate among men. All 5 male participants had been randomised to the zopiclone group, 3 of whom dropped out, and it was decided to perform the analyses on women only (n = 18).
Selective reporting (reporting bias)	Low risk	Comment: Unlikely
Other bias	High risk	Comment: Role of funding source not explicitly described.

Peles 2007

Methods	**Study design:** Randomised controlled trial **Study grouping:** Cross-over **Blinding:** Double **Duration:** 6 weeks Single-centre
Participants	**Baseline characteristics** Not reported for each group because of cross-over design.

Peles 2007 *(Continued)*

	Most (70%) of the 80 study participants were male. The mean age during study was 42.6 years, and the mean duration in MMT was 4.4 years. Almost half (48.8%) of the participants had other drug abuse in addition to benzodiazepines in the month prior to study entry. Specifically, 25 had positive urine for opiates, 12 for cocaine, 14 for cannabis, and 5 for amphetamines. With respect to lifetime psychiatric diagnosis, 9 participants (11.3%) had 1 of the psychotic disorders, 18 (22.5%) had an affective disorder, 8 (10%) had an adjustment disorder, 2 (2.5%) had an organic brain disorder, 38 (47.5%) had no DSM-IV Axis I diagnosis (but all 38 had a DSM-IV Axis II personality disorder), and 5 (6.3%) had no DSM-IV Axis I or Axis II psychiatric diagnosis. **Inclusion criteria:** All patients who were admitted to the MMT clinic between July 1993 and July 2004 were eligible for inclusion in the study. This MMT clinic receives patients who meet DSM-IV criteria for opioid dependence and report self administration of illicit heroin for 1 year or more. **Exclusion criteria:** None **Pretreatment:** No significant group differences
Interventions	**Intervention characteristics** Benzodiazepine taper schedule: run-in phase: taper, until reaching 6 mg/day clonazepam or equivalent. Week 1 through 6: 0.5 mg/week dose reduction 1. Benzodiazepine taper schedule + melatonin 5 mg/d (N = 40) 2. Benzodiazepine taper schedule + placebo (N = 40)
Outcomes	• Benzodiazepine cessation • Serious adverse events • Insomnia, PSQI • Relapse to benzodiazepine use
Identification	**Sponsorship source:** The study was supported (in part) by a grant from The Israel Anti Drug Authority. **Country:** Israel **Setting:** Outpatients in methadone maintenance treatment **Declarations of interest:** Not mentioned **Author's name:** Einat Peles **Institution:** Adelson Clinic, Tel Aviv Sourasky Medical Center **Email:** einatp@tasmc.health.gov.il **Address:** Adelson Clinic, Tel Aviv Sourasky Medical Center, 1 Henrietta Szold Street, Tel Aviv 64924, Israel
Notes	Only data from the first period (first 6 weeks) of this cross-over trial was included.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Not sufficiently described
Allocation concealment (selection bias)	Low risk	Quote: "consecutive container numbers" Comment: Done

Peles 2007 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "codes for melatonin first/placebo first were known only to the pharmacist" Comment: What has been done to ensure blinding of participants and study personnel is not described.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The codes for melatonin first/placebo first were known only to the pharmacist who prepared the sequence in a random manner and identified it to us only at the end of the study" Comment: Only pharmacist knew the code - done.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "40 patients who started on melatonin and 40 patients who started on placebo. Sixty-one patients (31 from the 'melatonin-first' group and 30 from the 'placebo-first' group) completed phase one (6 weeks). Forty-four patients completed all 13 weeks of the study, with no differences between groups (60% of the 40 'melatonin-first' group and 50% of the 40 'placebo-first' group (P = 0.5)." Comment: Unclear how the high dropout after 6 weeks affected the results
Selective reporting (reporting bias)	Unclear risk	Comment: The division of benzodiazepine continuers/discontinuers in the analysis seems to blur the effect of the study medication in itself.
Other bias	Low risk	Comment: No other apparent source of bias

Rickels 1999

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Blinding:** Double **Duration:** 13 weeks Single-centre
Participants	**Baseline characteristics** No group difference. Only combined baseline characteristics reported: • Age, mean (SD): 47 (12) • Male, N (%): 38 (49) • Employed: 51% • Duration of benzodiazepine treatment, months: 83 (75) • Benzodiazepine daily dose, mg diazepam equivalents: 19 (16.7) **Inclusion criteria:** Age range of 21 to 70 years, had to have been on continuous daily treatment with diazepam, lorazepam, or alprazolam for a minimum of 1 year, and needed to be able to provide written informed consent **Exclusion criteria:** A screening medical history, physical examination, ECG, blood count, blood chemistry, urine analysis, and urine drug screens were performed to confirm each patient's study eligibility. **Pretreatment:** No significant group differences
Interventions	**Intervention characteristics**

Rickels 1999 *(Continued)*

	Benzodiazepine taper schedule: gradual taper was initiated at approximately 25% reduction per week, with participants on lower therapeutic benzodiazepine doses possibly being tapered slightly faster, and participants on higher therapeutic doses being tapered slightly slower, but not longer than 6 weeks. After the taper was completed, participants were seen weekly for at least 5 weeks in order to determine their ability to stay off their benzodiazepine. During that time, participants continued to receive their double-blind study medication. Study medication was discontinued at 5 weeks' post-taper completion. From 5 to 12 weeks post-taper, participants left the program and returned to their private physician for doctor's choice management. 1. Benzodiazepine taper schedule + valproate 500 to 2500 mg/day(N = 19) 2. Benzodiazepine taper schedule + trazodone 100 to 500 mg/day(N = 41) 3. Benzodiazepine taper schedule + placebo(N = 18)
Outcomes	• Benzodiazepine withdrawal symptoms: Physician Withdrawal Checklist • Benzodiazepine cessation • Anxiety: HAM-A • Non-serious adverse events • Relapse to benzodiazepine use • Discontinuation due to adverse events
Identification	**Sponsorship source:** This study was supported by USPHS Research Grant MHO8957. **Country:** USA **Setting:** Outpatients **Declarations of interest:** The study was supported by a US Public Health Service research grant **Author's name:** Rickels K **Institution:** Mood and Anxiety Disorders Section, Department of Psychiatry, University of Pennsylvania **Email:** **Address:** University Science Center, 3600 Market Street, Suite 803, Philadelphia, PA 19104-2649, USA
Notes	We selected only the valproate vs placebo comparison for this meta-analysis because we did not consider it relevant to combine the experimental intervention groups into a single group (cf. *Cochrane Handbook* 16.5.4 on how to include multiple groups from 1 study).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Not described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "randomly assigned under double blind conditions to study drug or placebo." Comment: What has been done to ensure blinding of participants and study personnel is not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Not sufficiently described

Rickels 1999 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 15 participants, 5 trazodone (12.2%), 5 valproate (26.3%), and 5 placebo (27.7%), dropped out during the pretreatment phase. The 15 dropouts were compared on a variety of demographic and illness variables with the 63 participants who entered taper, and no significant differences were present.
Selective reporting (reporting bias)	Low risk	Comment: No apparent selective outcome reporting
Other bias	Unclear risk	Comment: Groups were not of equal size. No argument is provided.

Rickels 2000

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Blinding:** Double **Duration:** 11 to 13 weeks Single-centre
Participants	**Baseline characteristics** No significant differences between the groups; only data for the combined participant group reported: • Male, N (%): 59 (55) • Age, mean (SD): 48 (14) • Months of benzodiazepine use, mean (SD): 102 (92) **Inclusion criteria:** Participants were required to have a diagnosis of generalised anxiety disorder according to DSM-III-R, to be at least 21 years old, and to have been taking diazepam, lorazepam, or alprazolam in therapeutic doses continuously for the past 12 months. **Exclusion criteria:** Panic disorder diagnosis **Pretreatment:** No significant group differences
Interventions	**Intervention characteristics** Benzodiazepine taper schedule: 4-week stabilisation phase, 4- to 6-week taper phase: 25% reduction per week, 5-week benzodiazepine-free phase, the experimental drug continued for the first 3 weeks of the benzodiazepine-free phase 1. Benzodiazepine taper schedule + imipramine 180 mg/d(N = 23) 2. Benzodiazepine taper schedule + buspirone 38 mg/d(N = 28) 3. Benzodiazepine taper schedule + placebo(N = 24)
Outcomes	• Benzodiazepine cessation • Non-serious adverse events • Discontinuation due to adverse events • Serious adverse events
Identification	**Sponsorship source:** Supported by NIMH grant MH-08957. Dr Greenblatt was supported by NIMH grant MH-34223 and grant DA-05258 from the National Institute on Drug Abuse. The medications used were provided by Bristol-Myers Squibb CNS Group, Wallingford, CT. **Country:** USA

Rickels 2000 *(Continued)*

	Setting: Outpatients **Declarations of interest:** Not mentioned **Authors name:** Karl Rickels **Institution:** Mood and Anxiety Disorders Section, Department of Psychiatry, University of Pennsylvania, Philadelphia **Email:** krickels@mail.med.upenn.edu **Address:** University Science Center, 3600 Market St., Suite 803, Philadelphia, PA 19104
Notes	Adverse events not reported appropriately for a meta-analysis. We selected only the imipramine versus placebo comparison for this meta-analysis because we did not consider it relevant to combine the experimental intervention groups into a single group (cf. *Cochrane Handbook* 16.5.4 on how to include multiple groups from 1 study).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Not described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Medication was prepared double blind in identical capsules containing either 5 mg buspirone, 25 mg imipramine, or placebo" Comment: Sufficiently done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: Not clearly described
Selective reporting (reporting bias)	Low risk	Comment: Probably not, relevant outcome measures
Other bias	Low risk	Comment: No other sources of bias evident.

Romach 1998

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Blinding:** Double **Duration:** 6 weeks Single-centre

Romach 1998 *(Continued)*

Participants	**Baseline characteristics** Ondansetron • Male, N (%): 29 (62) • Age, mean (SD): 46 (13) • Months of benzodiazepine use: 62 (53) • Benzodiazepine dose (diazepam equivalents), mean (SD): 16 (13) Placebo • Male, N (%): 29 (58) • Age, mean (SD): 48 (13) • Months of benzodiazepine use: 74 (67) • Benzodiazepine dose (diazepam equivalents), mean (SD): 9 (7) **Inclusion criteria:** DSM-III-R criteria for benzodiazepine dependence, a desire to discontinue use of benzodiazepines, daily use of alprazolam or lorazepam for > 3 months **Exclusion criteria:** Dosage of lorazepam > 8 mg/day or alprazolam > 5 mg/day, psychoactive substance use disorder (other than benzodiazepines), using other prescribed psychotropic medications (other benzodiazepine, antidepressants, antipsychotics, or anticonvulsants), psychosis, moderate to severe major depression, significant cognitive impairment, or suicidal ideation. Serious medical illness, pregnancy, liver enzymes elevated more than 3 times the upper limit, past history of head trauma **Pretreatment:** More anxiety patients in the placebo group
Interventions	**Intervention characteristics** Benzodiazepine taper schedule: participants set their benzodiazepine tapering goals weekly with a study team member; the overall goal was benzodiazepine discontinuation within the treatment period (6 weeks). 1. Benzodiazepine taper schedule + ondansetron 4 mg/d(N = 54) 2. Benzodiazepine taper schedule + placebo(N = 54)
Outcomes	• Benzodiazepine withdrawal symptoms, Clinical Institute Withdrawal Assessment Scale - Benzodiazepines • Benzodiazepine mean dose • Anxiety, Symptom Checklist-90 anxiety subscale • Non-serious adverse events • Discontinuation due to adverse events
Identification	**Sponsorship source:** The study was supported in part by Glaxo Wellcome Canada. **Country:** Canada **Setting:** Outpatients **Declarations of interest:** Not mentioned **Author's name:** Myroslav Romach **Institution:** Departments of Pharmacology, Medicine, and Psychiatry and Faculty of Pharmacy, University of Toronto and Addiction Research Foundation, Toronto, Ontario, Canada **Email:** **Address:** Women's College Hospital, Department of Psychiatry, 76 Grenville St., Toronto, Ontario, Canada M5S 1B2

Romach 1998 *(Continued)*

Notes	Not possible to extract results from this study due to poor reporting

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Not described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: Described as double-blind and identical-appearing capsules
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Not specifically described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: Out of 108 participants, only 11 (10%) participants dropped out. However, it is unclear if dropout was balanced between groups.
Selective reporting (reporting bias)	Low risk	Comment: No protocol available, but no reason to suspect selective outcome reporting.
Other bias	High risk	Comment: Role of medicinal company as funding source not sufficiently described.

Rynn 2003

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Blinding:** Double **Duration:** 13 weeks Single-centre
Participants	**Baseline characteristics** No significant differences between groups; only data for the combined participant group reported: • Months of benzodiazepine use, mean (SD): 75 (64) • Male, N (%): 21 (52) **Inclusion criteria:** A diagnosis of panic disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition, at least 21 years old, and have been taking diazepam, lorazepam, or alprazolam in therapeutic doses continuously for at least the past 12 months (5 mg diazepam was considered equivalent to 1 mg lorazepam and 0.5 mg alprazolam). Individuals must also have expressed a desire to stop benzodiazepine intake. **Exclusion criteria:** Other psychotropic medication than benzodiazepines

Rynn 2003 *(Continued)*

	Pretreatment: No significant group differences
Interventions	**Intervention characteristics** Benzodiazepine taper schedule: after being kept on a stable benzodiazepine dose for 2 to 4 weeks within the therapeutic range during the screening period, participants were assigned to double-blind treatment during which time their benzodiazepine intake was not altered. This pretreatment lasted 4 weeks, after which participants were tapered from their benzodiazepine dose over a 6-week period. Benzodiazepine intake was reduced at the rate of 25% per week. Taper was followed by a 5-week benzodiazepine-free phase designed to prospectively assess the participant's clinical status in the initial period while being off benzodiazepines. Double-blind study treatment was continued for the first 3 weeks of this phase. For the last 2 weeks, placebo was substituted for imipramine and buspirone. 1. Benzodiazepine taper schedule + imipramine 180 mg/d(N = 18) 2. Benzodiazepine taper schedule + buspirone 32 mg/d(N = 12) 3. Benzodiazepine taper schedule + placebo(N = 10)
Outcomes	• Benzodiazepine withdrawal symptoms, Physician Withdrawal Checklist, Covi Withdrawal Cluster of the Hopkins Symptom Checklist • Benzodiazepine cessation • Anxiety: HAM-A (change from baseline) • Non-serious adverse event • Discontinuation due to adverse events
Identification	**Sponsorship source:** This research was supported by NIMH grant MH-08957. Bristol-Myers Squibb CNS Group (Wallingford, CT) provided all double-blinded medications. **Country:** USA **Setting:** Outpatients **Declarations of interest:** Not mentioned **Authors name:** Moira Rynn **Institution:** Mood and Anxiety Disorders Section, Department of Psychiatry, University of Pennsylvania, Suite 670, 3535 Market Street, Philadelphia, PA 19104-3309 **Email:** mrynn2@mail.med.upenn.edu **Address:** Mood and Anxiety Disorders Section, Department of Psychiatry, University of Pennsylvania, Suite 670, 3535 Market Street, Philadelphia, PA 19104-3309
Notes	Adverse events not appropriately described. We included only the imipramine-placebo comparison in the meta-analysis because we did not consider it relevant to combine the experimental intervention groups into a single group (cf. *Cochrane Handbook* 16.5.4 on how to include multiple groups from 1 study).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Not described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described

Rynn 2003 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Medication was prepared double blind in identical capsules" Comment: Done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Double-blind identical capsules - doneNot described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Of 52 patients randomised to 3 treatment conditions, 12 patients did not complete the pretreatment phase and 40 patients entered taper. The 2 patient groups did not differ in any baseline demographic or clinical measures with 1 exception. Dropouts had lower BZ doses at baseline, ex- pressed in diazepam equivalents, than patients entering taper (12.1 ± 7.7 versus 25.7 ± 19.5; F = 5.52; df = 1.50; P < 0.02). Dropouts also did not differ from taper patients in treatment assignment (2 = 0.69; df = 2; P = NS) or type of BZ at baseline (2 = 1.43; df = 2; P = NS). The main reason for dropping out of the program during the pre taper phase were adverse events (2 buspirone, 2 imipramine, and 1 placebo)." Comment: Acceptable and no difference between groups
Selective reporting (reporting bias)	Low risk	Comment: Protocol not available but no obvious selective outcome reporting
Other bias	Low risk	Comment: Role of BMS only to provide double-blinded study medication

Saul 1989

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Blinding:** Double **Duration:** 18 weeks Multicentre
Participants	**Baseline characteristics** Atenolol • Male, N (%): 19 (31) • Age, mean: 43.55 Placebo • Male, N (%): 22 (37) • Age, mean: 44.35 **Inclusion criteria:** 18 to 60 years old, daily use of benzodiazepines for at least 8 weeks, not more than 15 mg of diazepam **Exclusion criteria:** Cerebrovascular or generalised vascular disease, heart block, thyrotoxicosis, premenstrual tension or other trigger of cyclical anxiety and depression, pregnancy, antihypertensive therapy or any drug likely to affect anxiety, and those for whom diazepam would be an unsuitable rescue

Saul 1989 *(Continued)*

	Pretreatment: None reported.
Interventions	**Intervention characteristics** Benzodiazepine taper schedule: follow-up visits at 4-week intervals, participants should have stopped taking benzodiazepines by their 4th visit 1. Benzodiazepine taper schedule + atenolol 50 mg/d(N = 62) 2. Benzodiazepine taper schedule + placebo(N = 59)
Outcomes	• Benzodiazepine consumption • Anxiety • Withdrawal symptoms
Identification	**Sponsorship source:** Not described **Country:** UK **Setting:** Outpatients **Declarations of interest:** Not mentioned **Authors name:** Saul PA **Institution:** General Practitioners, Stuart Clinical Research Group **Email:** **Address:** P. A. Saul, 555 Chorley Old Road, Bolton, Lancashire, BL2 6AF, UK
Notes	None of the results were reported with mean and SD.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Not described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: Described as double-blind and matching placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: High dropout rate: 59 out of 121 withdrew (48.7%)
Selective reporting (reporting bias)	Low risk	Comment: No apparent selective outcome reporting
Other bias	Low risk	Comment: Apparently no other bias

Schweizer 1991

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Blinding:** Blinding **Duration:** 8 to 10 weeks Single-centre
Participants	**Baseline characteristics** No significant differences between the intervention groups, therefore combined group reported: • Male, N (%): 39 (48) • Age, mean (SD): 47 (15) **Inclusion criteria:** 18 years or older and receiving a daily dose of benzodiazepine continuously for at least the past year. Individuals were entered directly into the study if they were taking diazepam, alprazolam, or lorazepam in a dose of 40 mg or less diazepam equivalents (5 mg of diazepam = 0.5 mg of alprazolam = 1.0 mg of lorazepam). 6 individuals who were receiving a different benzodiazepine were switched to diazepam in an equivalent dose and stabilised for 3 weeks before entry into the study. **Exclusion criteria:** A history in the past year of alcohol or substance abuse or dependence, any acute or unstable medical condition, or not practicing adequate contraception **Pretreatment:** No significant group differences
Interventions	**Intervention characteristics** Benzodiazepine taper schedule: 1 to 2 weeks pretreatment, benzodiazepine taper was initiated at a rate of 25% per week and completed over 4 weeks. Once the taper phase was completed and the participant had discontinued benzodiazepine intake, treatment with carbamazepine or placebo was continued for 2 to 4 weeks, then discontinued abruptly. 1. Benzodiazepine taper schedule + carbamazepine, 200 to 800 mg/d(N = 27) (only 19 entered the benzodiazepine taper phase) 2. Benzodiazepine taper schedule + placebo(N = 28) (only 21 entered the benzodiazepine taper phase)
Outcomes	• Benzodiazepine withdrawal symptoms: Patient Withdrawal Checklist • Benzodiazepine cessation
Identification	**Sponsorship source:** This investigation was supported by Public Health Service research grant MH-08957, Washington, DC. **Country:** USA **Setting:** Outpatients **Declarations of interest:** Not mentioned **Author's name:** Edward Schweizer **Institution:** Psychopharmacology Research Unit, Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia **Email:** **Address:** 203 Piersol Bldg, Hospital of the University of Pennsylvania, 3400 Spruce St, Philadelphia, PA 19104

Schweizer 1991 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Not described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "random and double-blind fashion", "Carbamazepine was provided in capsules that were identical to the placebo" Comment: Done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Carbamazepine levels were obtained in 12 of 19 patients, with the treating psychiatrist kept blind to the results." Comment: Judged as done since treating psychiatrist was kept blind
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: Total dropout rate 15/55 (27%), 8 (30%) in the carbamazepine group and 7 (25%) in the placebo group
Selective reporting (reporting bias)	Low risk	Comment: No obvious selective outcome reporting
Other bias	Low risk	Comment: No other obvious sources of bias

Schweizer 1995

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Blinding:** Double **Duration:** 10 weeks Single-centre
Participants	**Baseline characteristics** Not reported **Inclusion criteria:** At least 18 years of age and taking diazepam, lorazepam, or alprazolam on a continuous daily basis for at least 1 year **Exclusion criteria:** Individuals were excluded from the study if they had a history of alcohol or substance abuse or dependence in the past year, or if they had any acute or unstable medical condition. Men could be of any age, while women had to be at least 2 years' postmenopause, or to have undergone an ovariectomy. **Pretreatment:** Unknown
Interventions	**Intervention characteristics**

Schweizer 1995 *(Continued)*

	Benzodiazepine taper schedule: 2 to 3 weeks pretreatment with experimental drug, taper at the rate of 25% per week, after completion of taper experimental drug was continued for 4 weeks, then abruptly discontinued 1. Benzodiazepine taper schedule + progesterone minimum 1200 mg/d (up to 3600 mg as tolerated) (N = 30) 2. Benzodiazepine taper schedule + placebo (N = 13)
Outcomes	• Benzodiazepine withdrawal symptoms, Physician Withdrawal Checklist • Benzodiazepine cessation • Anxiety, HAM-A • Non-serious adverse events: sedation
Identification	**Sponsorship source:** This study was supported by USPHS Research Grant MHO-8957. **Country:** USA **Setting:** Outpatients **Declarations of interest:** Not mentioned **Author's name:** Edward Schweizer **Institution:** University Science Center, Suite 803, 3600 Market Street, Philadelphia, PA 19104-2649, USA **Email:** **Address:** University Science Center, Suite 803, 3600 Market Street, Philadelphia, PA 19104-2649, USA
Notes	Benzodiazepine withdrawal symptoms and anxiety not reported appropriately.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Not described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "under random, double-blind conditions", "either micronized oral progesterone in 300 mg capsules or matched placebo" Comment: Described as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 8 (27%) participants in progesterone group versus 1 (8%) participant in placebo group dropped out during the pretreatment phase (due to sedation as side effect).
Selective reporting (reporting bias)	Low risk	Comment: No apparent selective outcome reporting
Other bias	Low risk	Comment: No apparent other bias

Tyrer 1981

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Blinding:** Double **Duration:** 2 weeks Multicentre
Participants	**Baseline characteristics** Not reported **Inclusion criteria:** Monotherapy with diazepam or lorazepam, medication use for at least 4 months regularly, and were thought not to require continued prescription **Exclusion criteria:** Drugs other than benzodiazepines **Pretreatment:** Not reported
Interventions	**Intervention characteristics** Benzodiazepine taper schedule: abrupt cessation 1. Benzodiazepines stopped and replaced by propranolol 20 mg x 3, increased to 40 mg x 3 if necessary(N = 20) 2. Benzodiazepines stopped and replaced by placebo(N = 20)
Outcomes	• Relapse to benzodiazepine use • Benzodiazepine withdrawal symptoms (authors' own scale, self rating of symptoms)
Identification	**Sponsorship source:** Not stated **Country:** UK **Setting:** General practice and outpatient psychiatric clinics **Declarations of interest:** Not mentioned **Authors name:** Peter Tyrer **Institution:** Mapperley Hospital, Nottingham, and Poisons Unit, New Cross Hospital, London **Email:** **Address:** Mapperley Hospital, Porchester Road, Nottingham NG3 6AA, UK
Notes	Figure 1 reports withdrawal symptoms in each group, only mean score not SD, and no other measures from which the SD can be calculated. Since this was the only identified study using propranolol, and since the scale for withdrawal symptoms was not a validated scale used in other included studies, it was not possible to safely impute values for SD. Otherwise only dropout rate was reported for each group (55% in placebo group and 36% in propranolol group) = patients returning to same benzodiazepine treatment as previously.

Risk of bias

Bias	Authors' judgement	Support for judgement

Tyrer 1981 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Comment: Not described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "If patients agreed to enter this double-blind study their benzodiazepines were stopped and replaced by propranolol or placebo tablets of identical appearance" Comment: Done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: Daily self ratings, no third party involved in outcome assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Of the 40 patients entering the study 18 (45%) dropped out during the two week period and took their benzodiazepine drugs again." Comment: High attrition rate
Selective reporting (reporting bias)	Low risk	Comment: No obvious selective outcome reporting
Other bias	High risk	Quote: "I.C.I. Pharmaceuticals Division for providing the propranolol and placebo tablets." Comment: Role, if any, in the analyses not described.

Tyrer 1996

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Blinding:** Double **Duration:** 12 weeks Single-centre
Participants	**Baseline characteristics** Dosulepin • Years of benzodiazepine use, median: 10 • Benzodiazepine dose (mg diazepam equivalent), mean: 8.0 Placebo • Years of benzodiazepine use, median: 10 • Benzodiazepine dose (mg diazepam equivalent), mean: 8.3 **Inclusion criteria:** Use of benzodiazepines for at least 6 months and had tried unsuccessfully to reduce or stop benzodiazepines due to apparent withdrawal symptoms, no other medication, written consent **Exclusion criteria:** Hypertension or the psychiatric diagnoses of major depressive disorder, a psychotic disorder, or melancholia

Tyrer 1996 *(Continued)*

	Pretreatment: Not reported
Interventions	**Intervention characteristics** Benzodiazepine taper schedule: reduction of the initial dosage by 20% every 2 weeks with the intention of stopping benzodiazepines entirely at week 8 1. Benzodiazepine taper schedule + dosulepin 150 mg/d(N = 41). 2. Benzodiazepine taper schedule + placebo(N = 46).
Outcomes	• Benzodiazepine cessation • Benzodiazepine withdrawal symptoms • Anxiety, HADS-A
Identification	**Sponsorship source:** Research Department of Boots Drug Company funded the study. **Country:** UK **Setting:** Outpatients **Declarations of interest:** Not mentioned **Authors name:** Peter Tyrer **Institution:** St Charles Hospital, London **Email:** **Address:** St Charles Hospital, London WlO 6DZ
Notes	For benzodiazepine withdrawal symptoms and anxiety, means were available from graphs only, but SDs were not reported. It was not possible to calculate SD from the presented data. Adverse events insufficiently reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Randomisation process not described.
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "under cover of randomly allocated dothiepin or placebo tablets...administered using double-blind procedure." Comment: What has been done to ensure blinding of participants and study personnel is not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Not sufficiently described
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "During the 14 weeks 45 patients (21 (51%) allocated to dothiepin and 24 (52%) to placebo) withdrew from the study." Comment: High attrition rate

Tyrer 1996 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: No apparent selective outcome reporting
Other bias	High risk	Comment: Funded by a drug company. Role of funding source not described.

Udelman 1990

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Blinding:** Double **Duration:** 6 to 12 weeks depending on the alprazolam starting dose Multicentre
Participants	**Baseline characteristics** Buspirone • Male, N (%): 17 (47) • Age, mean (range): 40 (24 to 62) • Number of benzodiazepine compounds: 1 (alprazolam only) Placebo • Male, N (%): 18 (50) • Age, mean (range): 44 (24 to 63) • Number of benzodiazepine compounds: 1 (alprazolam only) **Inclusion criteria:** 18 to 70 years of age, primary clinical anxiety, alprazolam pharmacotherapy for at least 3 months 0.75 to 3 mg daily, good physical health **Exclusion criteria:** Significant or uncontrolled organic disease, epilepsy or seizures, nursing/pregnant/not using contraceptive measures, substance use disorder, primary depression, panic disorder, psychosis, severe behaviour disorder, organic mental disorders, serious psychosomatic disorders, hypersensitivity to study drug, other drugs (psychotropics, beta-blockers, carbamazepine, clonazepam) within 1 month before start of the study **Pretreatment:** No significant pretreatment group differences
Interventions	**Intervention characteristics** Benzodiazepine taper schedule: 2 weeks of concurrent treatment (study drug + stable benzodiazepine dosage), from the third week tapering of alprazolam 0.5 mg/day each week until the total daily dose was 1.5 mg, after which the rate of tapering was 0.25 mg/day each week; completion of the tapering process was to take from 2 to 8 weeks depending on the alprazolam starting dose. At completion, participants were to continue receiving the study drugs (buspirone or placebo) for an additional 2 weeks. 1. Benzodiazepine taper schedule + buspirone 15 mg/d(N = 36) 2. Benzodiazepine taper schedule + placebo(N = 36)
Outcomes	• Benzodiazepine withdrawal symptoms: Abstinence Rating Scale • Benzodiazepine cessation • Adverse events • Anxiety: HAM-A • Discontinuation due to adverse events

Udelman 1990 *(Continued)*

Identification	**Sponsorship source:** Bristol-Myers Squibb **Country:** USA **Setting:** Outpatients **Declarations of interest:** Not mentioned **Authors name:** Harold D Udelman **Institution:** Biomedical Stress Research Foundation, Phoenix, Arizona, USA **Email:** Not available **Address:** Biomedical Stress Research Foundation, 45 East Born Road, Phoenix, Arizona 85012
Notes	Means only given in figures (HAM-A and benzodiazepine withdrawal symptoms), no SDs reported, not possible to impute in a methodologically valid way.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Not described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients meeting the selection criteria were randomly assigned to one of two groups to receive either buspirone or placebo...Both buspirone and placebo (indistinguishable in physical appearance) were to be administered at a fixed dose..." Comment: Placebo was described as indistinguishable in physical appearance.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Not sufficiently described
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: High attrition rate in buspirone group (42%) and in placebo group (53%)
Selective reporting (reporting bias)	Low risk	Comment: Protocol not available, but no indication of selective outcome reporting.
Other bias	High risk	Comment: Role of funding pharmaceutical company not described.

Vissers 2007

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Blinding:** Double **Duration:** 16 weeks (10 weeks to taper off and 6 weeks post-taper)

Vissers 2007 *(Continued)*

	9 general practices
Participants	**Baseline characteristics** Melatonin • Male, N (%): 6 (30) • Years of benzodiazepine use, 1 to 5 years: 7 (35%) • Years of benzodiazepine use, 6 to 9 years: 4 (20%) • Years of benzodiazepine use, >= 10 years: 9 (45%) • Age: < 50 years: 3 (15%), 50 to 59: 3 (15%), 60 to 69: 6 (30%), 70 to 79: 7 (35%), > 80: 1 (5%) • Benzodiazepine dose: low: 11 (55%), moderate: 4 (20%), high: 5 (25%) Placebo • Male, N (%): 10 (56) • Years of benzodiazepine use, 1 to 5 years: 7 (39%) • Years of benzodiazepine use, 6 to 9 years: 4 (22%) • Years of benzodiazepine use, >= 10 years: 6 (34%) • Age: < 50 years: 3 (17%), 50 to 59: 3 (17%), 60 to 69: 7 (39%), 70 to 79: 4 (22%), > 80: 1 (5%) • Benzodiazepine dose: low: 14 (78%), moderate: 0, high: 5 (25%) **Inclusion criteria:** Adult patients who used benzodiazepines as a sleeping medication for more than 3 months (defined as long-term use) at a minimum of 3 days per week **Exclusion criteria:** Use of more than 1 benzodiazepine at the same time, use of another type of sleep medication, use of stimulants and alcohol misuse (according to individual's GP), serious mental/somatic disease, or unfit to participate **Pretreatment:** No significant pretreatment differences
Interventions	**Intervention characteristics** Benzodiazepine taper schedule: the benzodiazepine dose was converted to an equivalent dose of diazepam, which was stabilised for 2 weeks and then further converted every 2 weeks to 75%, 50%, 25%, 12.5%, and 0% of the original dose. 1. Benzodiazepine taper schedule + melatonin 5 mg (4 hours before bed) (N = 20) 2. Benzodiazepine taper schedule + placebo (N = 18)
Outcomes	• Benzodiazapine cessation • Alcohol consumption • Relapse to benzodiazepine use • Insomnia
Identification	**Sponsorship source:** Not described **Country:** The Netherlands **Setting:** Outpatients in GP **Declarations of interest:** Not mentioned **Authors name:** Vissers FHJA **Institution:** Department of General Practice, Maastricht University **Email:** harry.crebolder@hag.unimaas.nl

Vissers 2007 *(Continued)*

	Address: Department of General Practice, Maastricht University, P.O. Box 616, Maastricht 6200 MD, the Netherlands
Notes	Insomnia: the Sleep Wake Experience List: mean and SD not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Not sufficiently described
Allocation concealment (selection bias)	Unclear risk	Comment: Not sufficiently described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The patients, their GPs and the principal investigator were blinded for the study medication." Comment: What has been done to ensure blinding of participants and study personnel is not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Insufficient information to judge the risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All randomised participants were analysed.
Selective reporting (reporting bias)	Unclear risk	Comment: Benzodiazepine withdrawal symptoms ambiguously reported.
Other bias	Low risk	Comment: No other apparent biases, funding not reported

Vorma 2011

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Blinding:** None - open-label **Duration:** 3 weeks of inpatient treatment Single-centre
Participants	**Baseline characteristics** Valproate • Male, N (%): 12 (86) • Age, mean (SD): 32 (6.7) • Employed, N (%): 0 • Years of opioid use, mean (SD): 11 (5.5) • Years of benzodiazepine use, mean (SD): 12 (7.1) • Benzodiazepine dose, mg (diazepam equivalent), median (range): 60 (20 to 160) Control

Vorma 2011 *(Continued)*

	• Male, N (%): 10 (62) • Age, mean (SD): 32 (5.3) • Employed, N (%): 3 (19) • Years of opioid use, mean (SD): 10 (4.6) • Years of benzodiazepine use, mean (SD): 9 (5.2) • Benzodiazepine dose, mg (diazepam equivalent), median (range): 30 (8 to 75) **Inclusion criteria:** DSM-IV criteria for opioid dependence and benzodiazepine dependence **Exclusion criteria:** Pregnancy, active medical illnesses or severe mental disorders, history of convulsions, or unable to speak Finnish **Pretreatment:** At baseline, the median diazepam-equivalent dose was 60 mg daily (range 20 to 160 mg) in the valproate group and 30 mg (range 8 to 75 mg) in the control group.
Interventions	**Intervention characteristics** Benzodiazepine taper schedule: reduction with 10 mg diazepam equivalents daily until 40 mg per day, after which reductions were 5 mg daily 1. Benzodiazepine taper schedule + valproate 20 mg/kg(N = 14) 2. Benzodiazepine taper schedule only (control group)(N = 16)
Outcomes	• Benzodiazepine withdrawal symptoms, Clinical Institute Withdrawal Assessment Scale - Benzodiazepines • Serious adverse events
Identification	**Sponsorship source:** The study was supported by Annual EVO Financing (special government subsidies) from the Department of Psychiatry, Helsinki University Central Hospital. No support was provided by any pharmaceutical company. **Country:** Finland **Setting:** Opioid maintenance treatment, inpatient setting, very rapid benzodiazepine-tapering regimen **Declarations of interest:** None **Author's name:** Helena Vorma **Institution:** Helsinki University Central Hospital, Department of Psychiatry **Email:** vorma@hus.fin **Address:** Helsinki University Hospital, Department of Psychiatry, P.O. Box 590, FI-00029 HUS, Finland
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Not described
Allocation concealment (selection bias)	Low risk	Quote: "To prevent unequal treatment group sizes, we used block randomisation in blocks of six subjects. Sealed envelopes were used to keep the randomisation sequence unknown. The study was carried out as an open trial, with all outcome ratings assessed blindly to prevent detection bias."

Vorma 2011 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: Not done, open-label trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: All outcome assessments were done blindly.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Another 8 subjects discontinued participation in CIWA-B ratings, but stayed in treatment." Comment: Not described why and from which group, accounted for by LOCF, but difficult to judge if this might give rise to any kind of bias
Selective reporting (reporting bias)	Unclear risk	Comment: No protocol available; despite the rapid benzodiazepine taper regimen, it is remarkable that there is no indication of the benzodiazepine-tapering success
Other bias	Unclear risk	Comment: Big difference in benzodiazepine dose between groups at baseline (valproate 60 mg/day, control group 30 mg/day)

Zhang 2013

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Blinding:** Unknown **Duration:** 3 months Single-centre
Participants	**Baseline characteristics** Trazodone • Male, N (%): 8 (40) • Age, mean (SD): 45.73 (9.51) • Years of benzodiazepine use, mean (SD): 2.20 (1.20) Placebo • Male, N (%): 8 (44) • Age, mean (SD): 44.92 (9.41) • Years of benzodiazepine use, mean (SD): 2.20 (1.10) **Inclusion criteria:** Benzodiazepine dependence syndrome (Criteria of Mental Disorders in China, Third Edition), insomnia **Exclusion criteria:** Abuse of alcohol or other psychoactive drugs, other mental disorders, serious somatic illness, allergic to study medication, suicidal risk, pregnancy, breastfeeding, lack of consent **Pretreatment:** No significant pretreatment group differences
Interventions	Benzodiazepine taper schedule: benzodiazepine reduced to half dosage, when participant has had stable sleep for 5 days, then dosage is halved again and so forth.

Zhang 2013 *(Continued)*

	1. Benzodiazepine taper schedule + trazodone 50 to 300 mg/day(N = 20) 2. Benzodiazepine taper schedule + placebo(N = 18)
Outcomes	• Benzodiazepine withdrawal symptoms: Withdrawal Symptoms Checklist • Anxiety: HAM-A
Identification	**Sponsorship source:** Not reported **Country:** China **Setting:** Outpatients **Declarations of interest:** Not mentioned **Author's name:** Zhang Hong-Ju **Institution:** He'nan Provincial People's Hospital, Zhengzhou **Email:** hongju_z@yahoo.com.cn **Address:** Department of Neurology, He'nan Provincial People's Hospital, Zhengzhou 450003, He'nan, China
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Not described
Allocation concealment (selection bias)	Unclear risk	Comment: Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: Not described as blinded or open-label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Not described as blinded or open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Attrition: 2 of 38 (5%) participants
Selective reporting (reporting bias)	High risk	Comment: No data on use of benzodiazepine at follow-up
Other bias	Low risk	Comment: No other apparent sources of bias

Zitman 2001

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group

Zitman 2001 *(Continued)*

	Blinding: Double **Duration:** 12 weeks Multicentre
Participants	**Baseline characteristics** Paroxetine • Male, N (%): 19 (27) • Age, mean (range): 55 (24 to 84) • Years of benzodiazepine use, mean (range): 5.5 (0.3 to 27) • Benzodiazepine dose, mg (diazepam equivalent), median (range): 9 (1 to 30) Placebo • Male, N (%): 36 (28) • Age, mean (range): 57 (25 to 84) • Years of benzodiazepine use, mean (range): 6.4 (0.3 to 25) • Benzodiazepine dose, mg (diazepam equivalent), median (range): 9 (0.5 to 60) **Inclusion criteria:** Benzodiazepine use for at least 3 months, a diagnosis of major depressive disorder (DSM-III-R), at least 18 years of age, written informed consent **Exclusion criteria:** Depression caused by organic factors, psychosis, schizophrenia, pregnancy, lactation, childbearing potential with a lack of adequate contraception, severe concomitant medical conditions, history of seizure disorders, use of other psychotropic medication during the 3 months prior to screening, clinically significant abnormalities in haematology or clinical chemistry, misuse of alcohol or illicit drugs, excessive use of benzodiazepines (more than 3 times the maximal dose), current suicidal risk **Pretreatment:** No significant pretreatment group differences
Interventions	**Intervention characteristics** Benzodiazepine taper schedule: weeks 1 to 4: transfer to diazepamweeks 5 to 10: constant dose; weeks 11 to 12: 25% reduction per week; weeks 13 to 14: 12.5% reduction in 4 steps to 0 1. Benzodiazepine taper schedule + paroxetine 20 mg/d(N = 70) 2. Benzodiazepine taper schedule + placebo(N = 129)
Outcomes	• Benzodiazepine withdrawal symptoms, BWSQ • Benzodiazepine cessation • Serious adverse events • Anxiety (Spielberger State-Trait Anxiety Inventory (STAI-DY1 and 2)) • Non-serious adverse events
Identification	**Sponsorship source:** One of the authors was employed by SmithKline Beecham, which also funded the study. **Country:** The Netherlands **Setting:** Outpatients **Declarations of interest:** Not mentioned **Authors name:** Frans Zitman **Institution:** Department of Psychiatry, Leiden and UMC Stat Radbond, Nijmegen **Email:** f.g.zitman@lumc.nl

Zitman 2001 *(Continued)*

	Address: Department of Psychiatry, Leiden, BIP, P.O. Box 9600, 2300 RC Leiden
Notes	Anxiety: Not sufficiently reported Withdrawal symptoms: Data not reported for placebo vs paroxetine, but for success vs no-success groups.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A randomisation list (1-330) in blocks of six was obtained by using the blocks of six was obtained by using the random number generator of SPSS/PC + (SPSS, 1997)." Comment: Done
Allocation concealment (selection bias)	Low risk	Quote: "Based on this list, study medication (paroxetine, placebo) was blister packed and wrapped by Genfarma, The Netherlands. Blocks were sequentially distributed to GPs. Unused blocks were reallocated. The list was kept by the Medical Adviser on Safety of the medical department Adviser on Safety of the medical department of SmithKline Beecham, The Netherlands." Comment: Done
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Patients were randomised to 20 mg of paroxetine or placebo in a 1:2 double-blind fashion" Comment: What was done to ensure blinding of participants and personnel in terms of matching paroxetine/placebo is not described.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "After the database was closed and basic descriptive analyses were done, the actual codes were added to the database" Comment: Done
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 50% completed the programme in the paroxetine group and 43% in the placebo group.
Selective reporting (reporting bias)	Unclear risk	Comment: Some outcome data not reported for randomisation groups, but for success and no-success group instead.
Other bias	High risk	Comment: Role of funding pharmaceutical company not described.

AEs: adverse events
BWSQ: Benzodiazepine Withdrawal Symptom Questionnaire
CI: confidence interval
CIWA-B: Clinical Institute Withdrawal Assessment Scale - Benzodiazepines
DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, Revised 3rd Edition
DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision
ECG: electrocardiogram
GAD: generalised anxiety disorder
GP: general practitioner
HADS-A Hospital Anxiety and Depression Scale - Anxiety subscale
HAM-A: Hamilton Anxiety Rating Scale
HAM-D: Hamilton Depression Rating Scale
ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th revision
ITT: intention-to-treat
IV: intravenous

LOCF: last observation carried forward
MADRS: Montgomery–Åsberg Depression Rating Scale
MMT: methadone maintenance treatment
NIMH: National Institute of Mental Health
NS: not specified
PSQI: Pittsburgh Sleep Quality Index
PTSD: post-traumatic stress disorder
PWC: Physician Withdrawal Checklist
SAEs: serious adverse events
SD: standard deviation
SE: standard error

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

Study	Reason for exclusion
Allain 1998	Wrong patient population: duration of benzodiazepine use above 1 month and no mention of dependence
Avedisova 2007	Wrong study design: not randomised
Bobes 2012	Wrong study design: uncontrolled, observational study
Bourgeois 2014	Wrong study design: uncontrolled, observational study
Cantopher 1990	Wrong study design: co-intervention not delivered equally in both intervention groups
Cohen-Mansfield 1999	Wrong study design: observational study
Declerck 1999	Wrong intervention: switch to benzodiazepine-like drug without discontinuation
Emara 2009	Wrong study design: not randomised
Garcia-Borreguero 1992	Wrong study design: not randomised
Hallstrom 1988	Wrong study design: co-intervention not delivered equally in both intervention groups
Isaka 2009	Wrong patient population: not chronic benzodiazepine users
Lahteenmaki 2014	Wrong patient population: not chronic benzodiazepine users
Lemoine 1997	Wrong study design: co-intervention not delivered equally in both intervention groups
Lopatko 2006	Wrong study design: not randomised
Nakajima 2007	Wrong study design: observational study
Petrovic 2002	Wrong study design: the study investigated gradual benzodiazepine withdrawal versus abrupt discontinuation
Rocco 1992	Wrong study design: not randomised
Rubio 2009	Wrong study design: observational study
Saxon 1997	Wrong study design: study not designed to evaluate benzodiazepine discontinuation
Shapiro 1995	Wrong intervention: switch to benzodiazepine-like drug without discontinuation

Study	Reason for exclusion
Vescovi 1987	Wrong study design: study not designed to evaluate benzodiazepine discontinuation
Weizman 2003	Wrong study design: not randomised

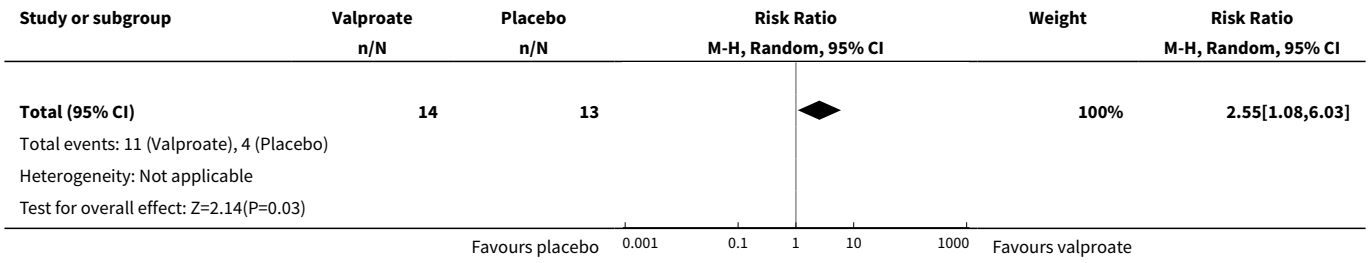
DATA AND ANALYSES

Comparison 1. Valproate versus placebo or no intervention

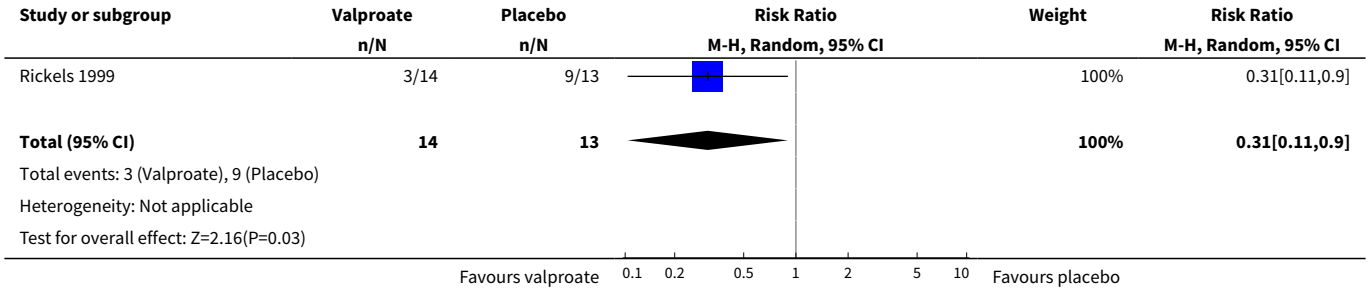
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Benzodiazepine discontinuation, end of intervention	1	27	Risk Ratio (M-H, Random, 95% CI)	2.55 [1.08, 6.03]
2 Relapse to benzodiazepine use, end of intervention	1	27	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.11, 0.90]
3 Benzodiazepine discontinuation, longest follow-up	1	24	Risk Ratio (M-H, Random, 95% CI)	1.57 [0.80, 3.09]
4 Relapse to benzodiazepine use, longest follow-up	1	24	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.13, 1.39]
5 Anxiety: HAM-A (Hamilton Anxiety Rating Scale), end of intervention	1	27	Mean Difference (IV, Random, 95% CI)	-0.40 [-6.47, 5.67]
6 Benzodiazepine withdrawal symptoms, end of intervention	2	56	Std. Mean Difference (IV, Random, 95% CI)	-0.15 [-0.68, 0.37]
6.1 Physician Withdrawal Checklist	1	27	Std. Mean Difference (IV, Random, 95% CI)	-0.01 [-0.77, 0.74]
6.2 CIWA-B (Clinical Institute Withdrawal Assessment Scale - Benzodiazepines)	1	29	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-1.01, 0.45]
7 Discontinuation due to adverse events	1	29	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8 Serious adverse events	1	29	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Valproate versus placebo or no intervention, Outcome 1 Benzodiazepine discontinuation, end of intervention.

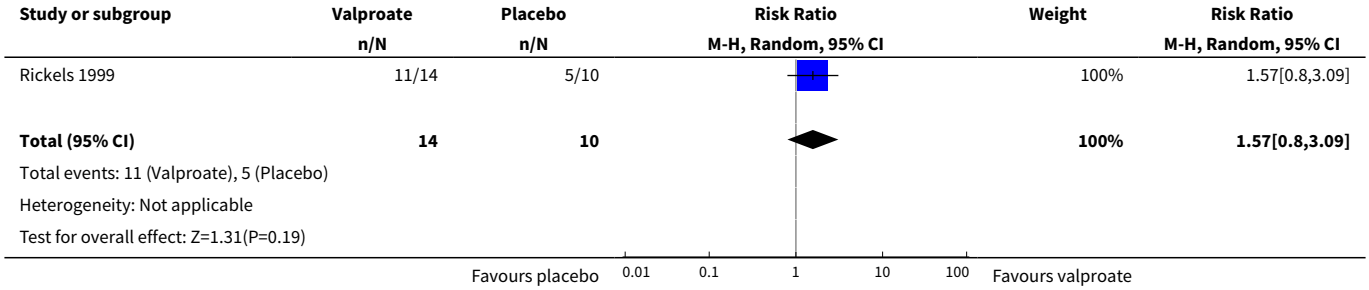
Study or subgroup	Valproate n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Rickels 1999	11/14	4/13		100%	2.55[1.08,6.03]



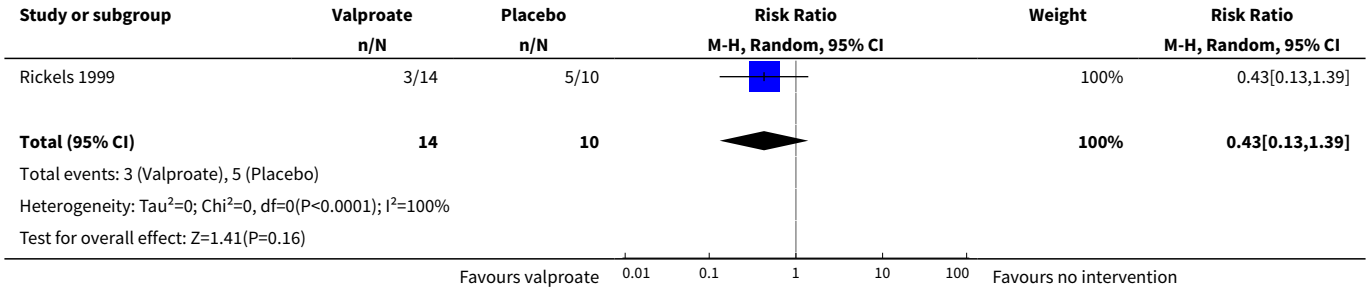
Analysis 1.2. Comparison 1 Valproate versus placebo or no intervention, Outcome 2 Relapse to benzodiazepine use, end of intervention.



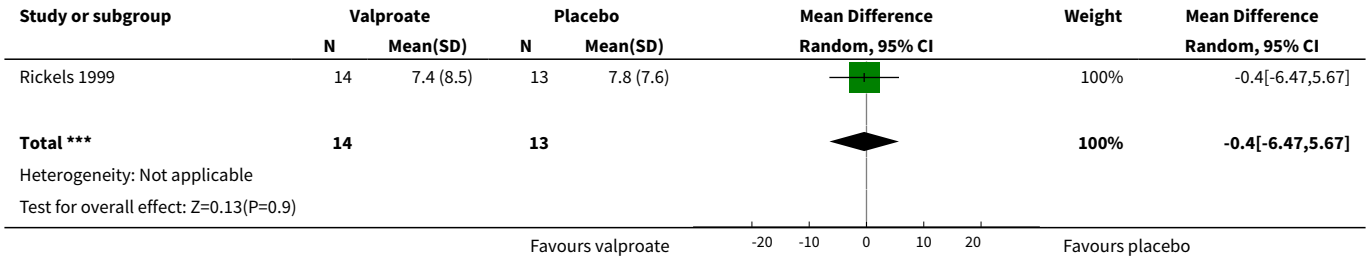
Analysis 1.3. Comparison 1 Valproate versus placebo or no intervention, Outcome 3 Benzodiazepine discontinuation, longest follow-up.



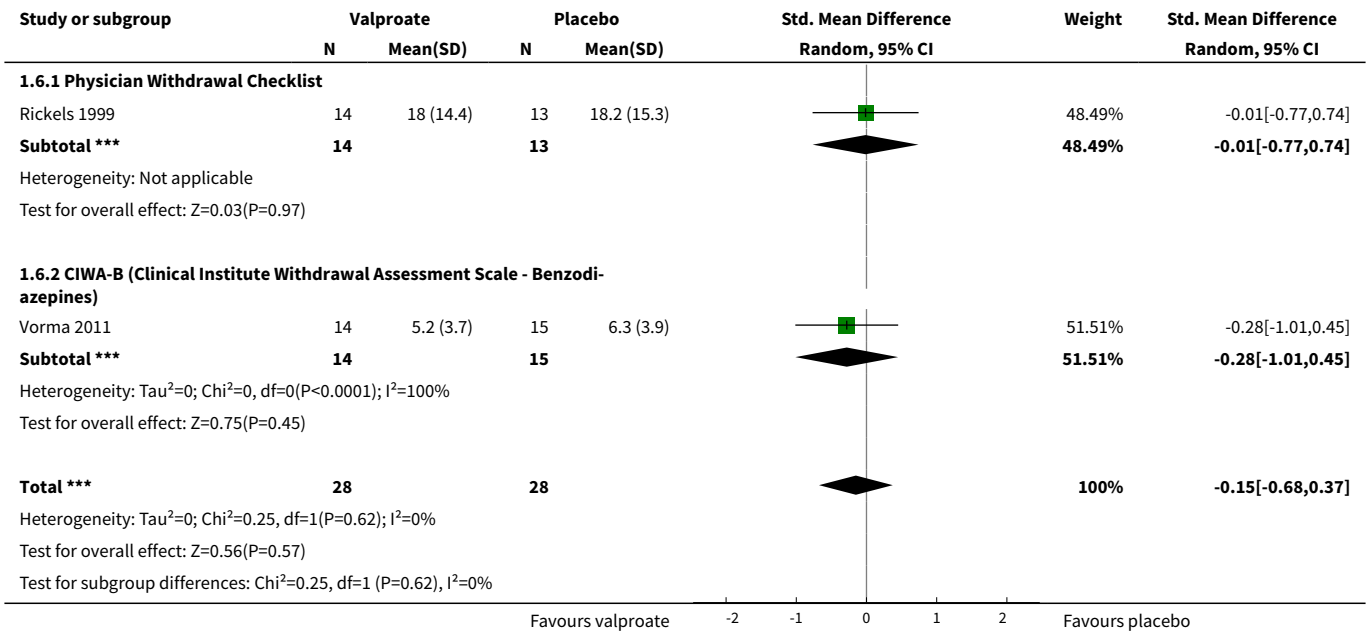
Analysis 1.4. Comparison 1 Valproate versus placebo or no intervention, Outcome 4 Relapse to benzodiazepine use, longest follow-up.



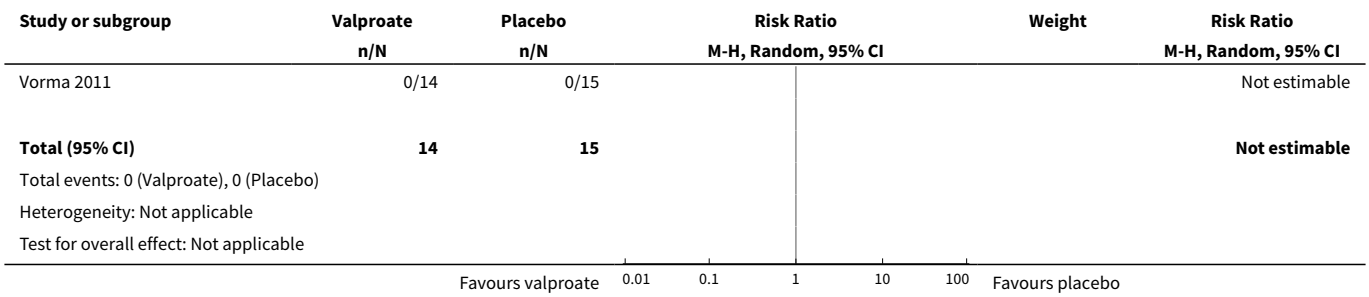
Analysis 1.5. Comparison 1 Valproate versus placebo or no intervention, Outcome 5 Anxiety: HAM-A (Hamilton Anxiety Rating Scale), end of intervention.



Analysis 1.6. Comparison 1 Valproate versus placebo or no intervention, Outcome 6 Benzodiazepine withdrawal symptoms, end of intervention.

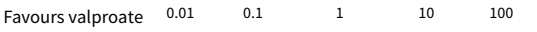


Analysis 1.7. Comparison 1 Valproate versus placebo or no intervention, Outcome 7 Discontinuation due to adverse events.



Analysis 1.8. Comparison 1 Valproate versus placebo or no intervention, Outcome 8 Serious adverse events.

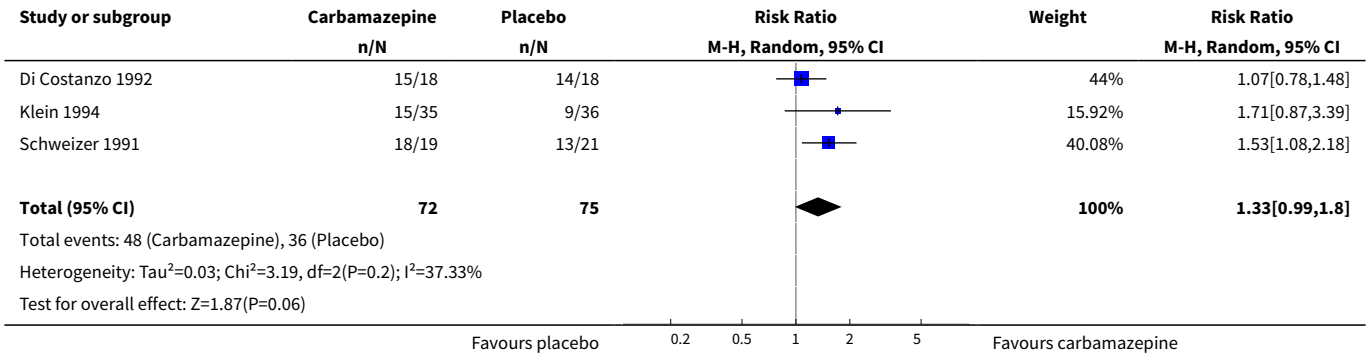
Study or subgroup	Valproate n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Vorma 2011	0/14	0/15			Not estimable
Total (95% CI)	**14**	**15**			**Not estimable**
Total events: 0 (Valproate), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



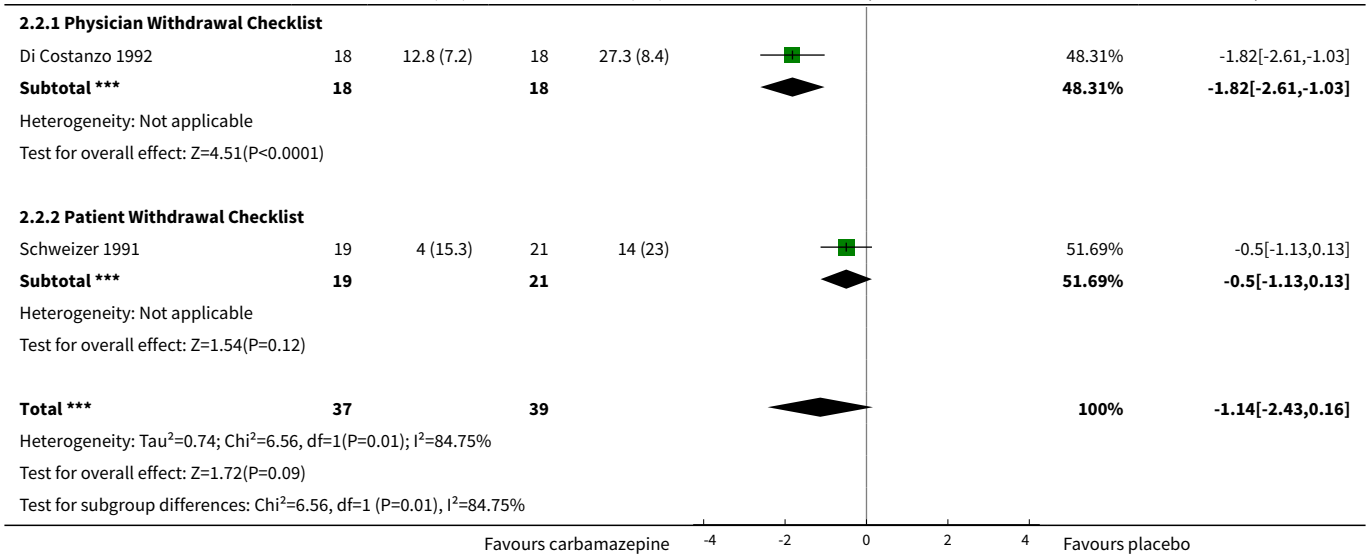
Comparison 2. Carbamazepine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Benzodiazepine discontinuation, end of intervention	3	147	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.99, 1.80]
2 Benzodiazepine withdrawal symptoms	2	76	Std. Mean Difference (IV, Random, 95% CI)	-1.14 [-2.43, 0.16]
2.1 Physician Withdrawal Checklist	1	36	Std. Mean Difference (IV, Random, 95% CI)	-1.82 [-2.61, -1.03]
2.2 Patient Withdrawal Checklist	1	40	Std. Mean Difference (IV, Random, 95% CI)	-0.50 [-1.13, 0.13]
3 Benzodiazepine discontinuation, longest follow-up	1	40	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.86, 2.29]
4 Relapse to benzodiazepine use	1	36	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.08, 1.44]
5 Serious adverse events	1	36	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Non-serious adverse events	1	36	Risk Ratio (M-H, Random, 95% CI)	7.0 [0.39, 126.48]
7 Anxiety, HAM-A	1	36	Mean Difference (IV, Random, 95% CI)	-6.0 [-9.58, -2.42]
8 Discontinuation due to adverse events	1	36	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

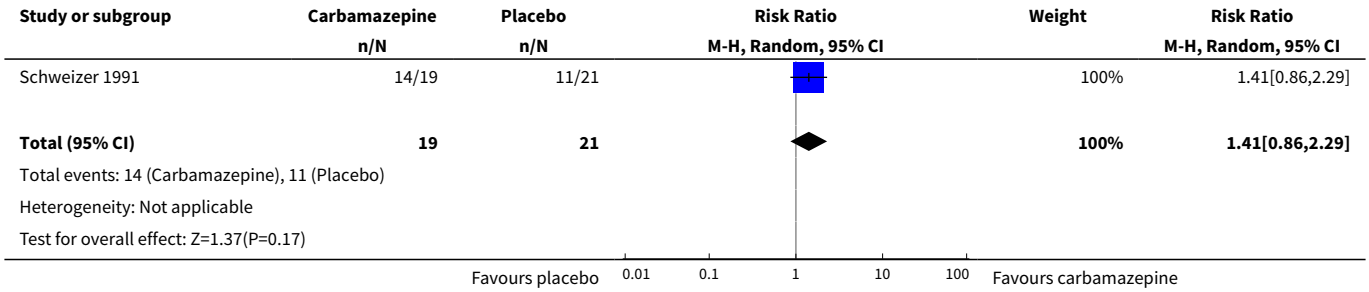
Analysis 2.1. Comparison 2 Carbamazepine versus placebo, Outcome 1 Benzodiazepine discontinuation, end of intervention.



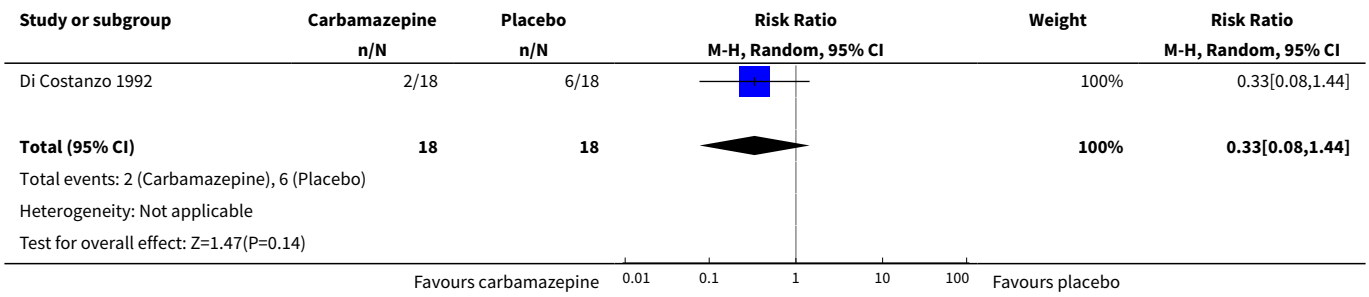
Analysis 2.2. Comparison 2 Carbamazepine versus placebo, Outcome 2 Benzodiazepine withdrawal symptoms.



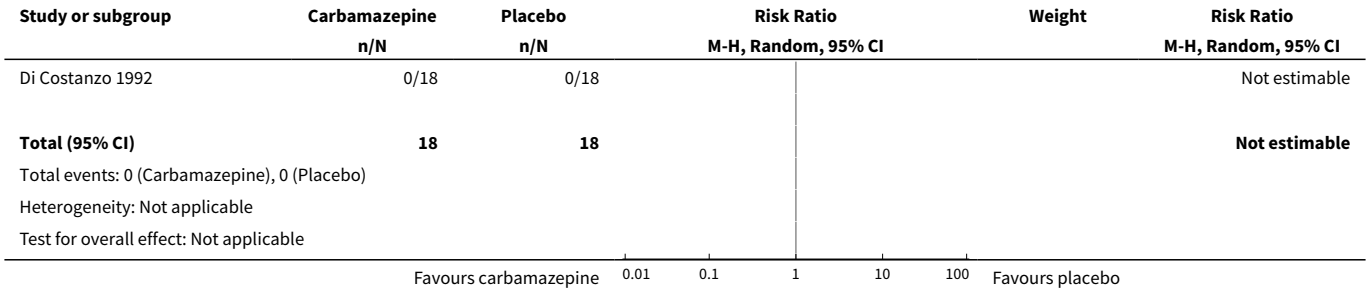
Analysis 2.3. Comparison 2 Carbamazepine versus placebo, Outcome 3 Benzodiazepine discontinuation, longest follow-up.



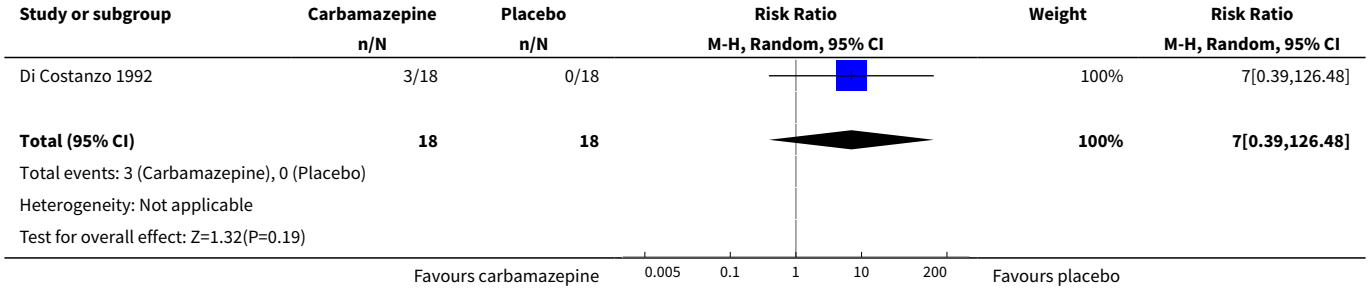
Analysis 2.4. Comparison 2 Carbamazepine versus placebo, Outcome 4 Relapse to benzodiazepine use.



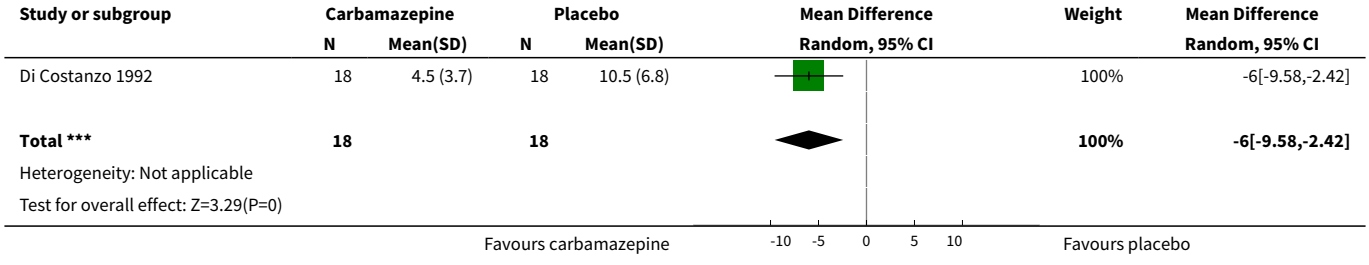
Analysis 2.5. Comparison 2 Carbamazepine versus placebo, Outcome 5 Serious adverse events.



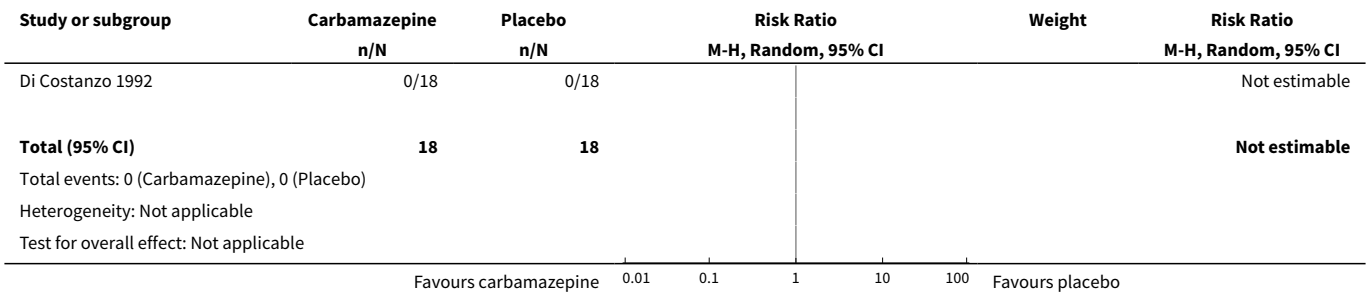
Analysis 2.6. Comparison 2 Carbamazepine versus placebo, Outcome 6 Non-serious adverse events.



Analysis 2.7. Comparison 2 Carbamazepine versus placebo, Outcome 7 Anxiety, HAM-A.



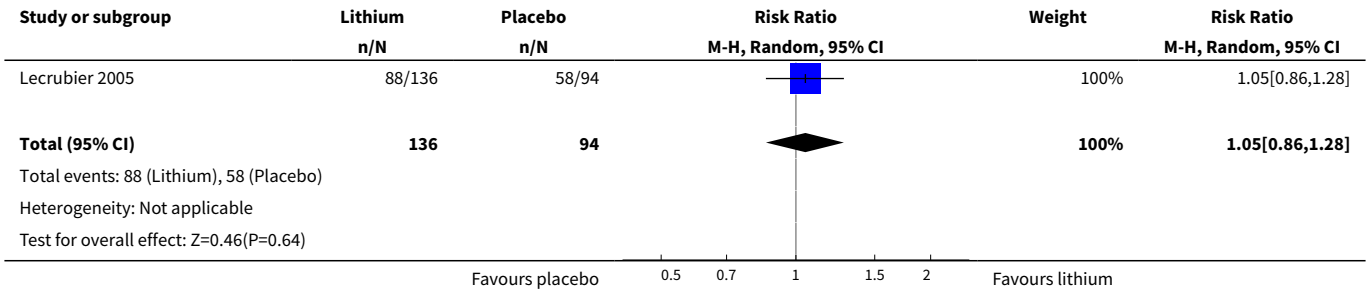
Analysis 2.8. Comparison 2 Carbamazepine versus placebo, Outcome 8 Discontinuation due to adverse events.



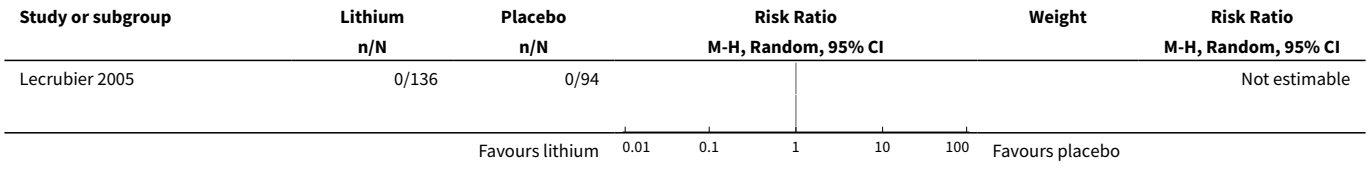
Comparison 3. Lithium versus placebo

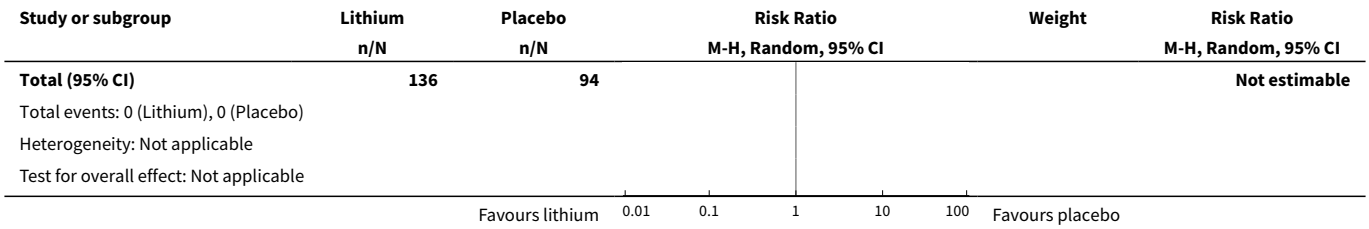
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Benzodiazepine discontinuation	1	230	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.86, 1.28]
2 Serious adverse events	1	230	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Non-serious adverse events	1	230	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.75, 1.49]
4 Discontinuation due to adverse events	1	230	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.13, 15.03]

Analysis 3.1. Comparison 3 Lithium versus placebo, Outcome 1 Benzodiazepine discontinuation.

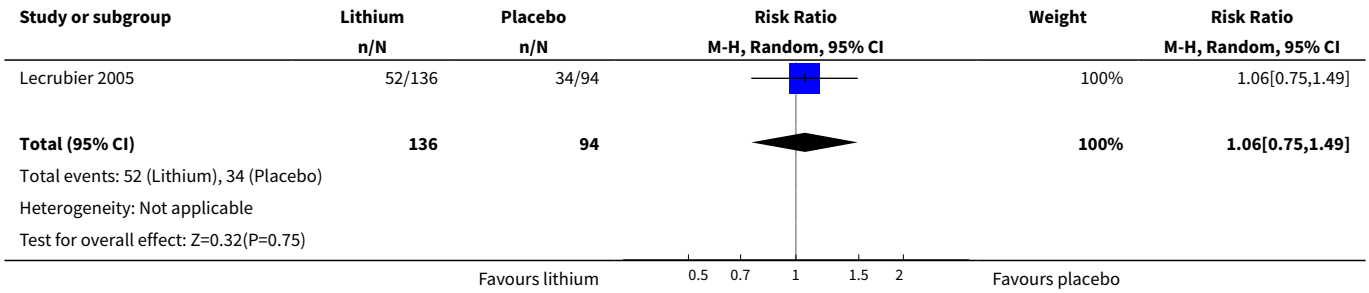


Analysis 3.2. Comparison 3 Lithium versus placebo, Outcome 2 Serious adverse events.

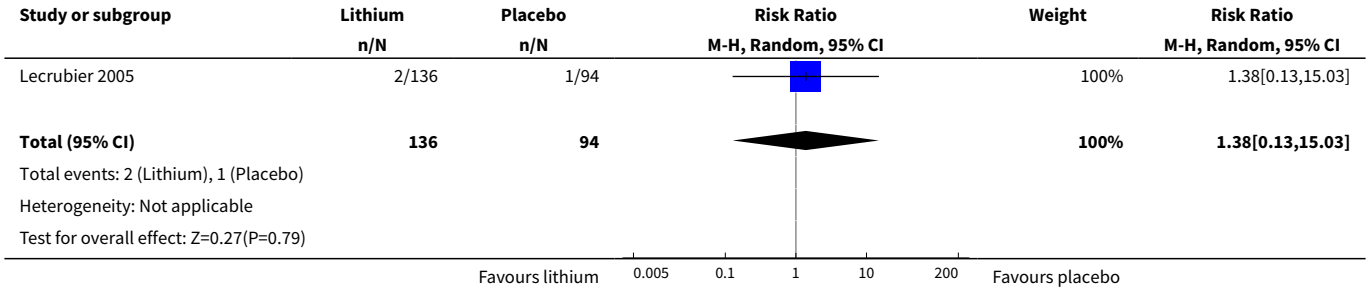




Analysis 3.3. Comparison 3 Lithium versus placebo, Outcome 3 Non-serious adverse events.



Analysis 3.4. Comparison 3 Lithium versus placebo, Outcome 4 Discontinuation due to adverse events.

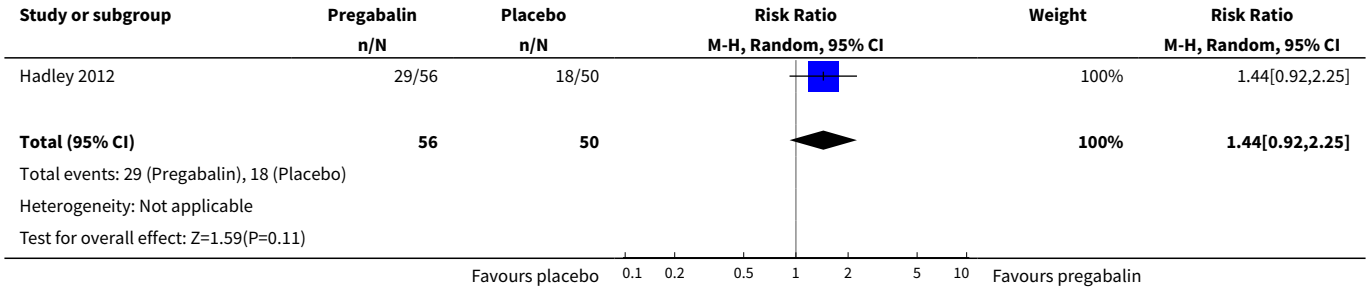


Comparison 4. Pregabalin versus placebo

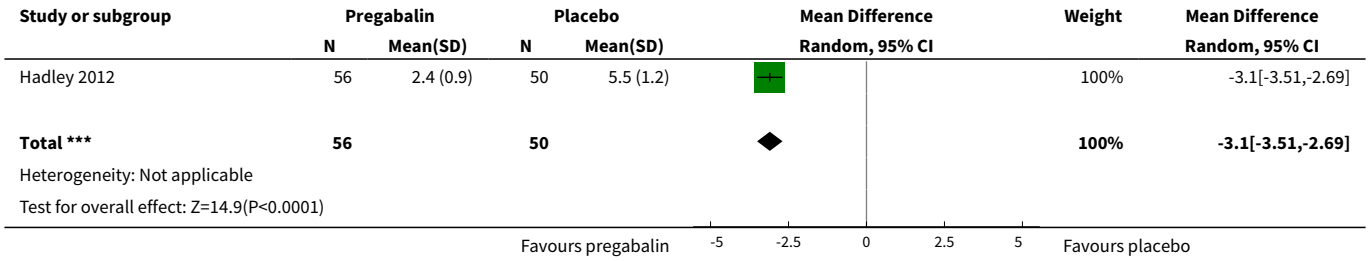
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Benzodiazepine discontinuation, end of intervention	1	106	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.92, 2.25]
2 Benzodiazepine withdrawal symptoms (Physician Withdrawal Checklist), end of intervention	1	106	Mean Difference (IV, Random, 95% CI)	-3.1 [-3.51, -2.69]
3 Anxiety, HAM-A, end of intervention	1	106	Mean Difference (IV, Random, 95% CI)	-4.8 [-5.28, -4.32]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Serious adverse events	1	106	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.16, 2.85]
5 Non-serious adverse events	1	106	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.84, 1.40]
6 Discontinuation due to adverse events	1	106	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.31, 2.59]

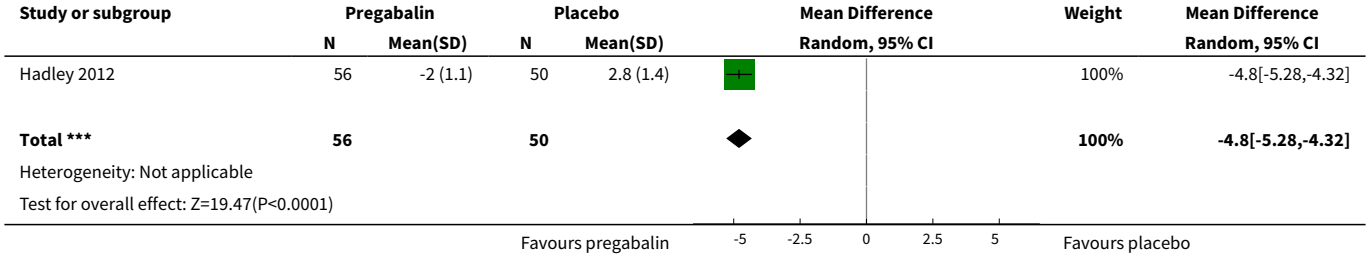
Analysis 4.1. Comparison 4 Pregabalin versus placebo, Outcome 1 Benzodiazepine discontinuation, end of intervention.



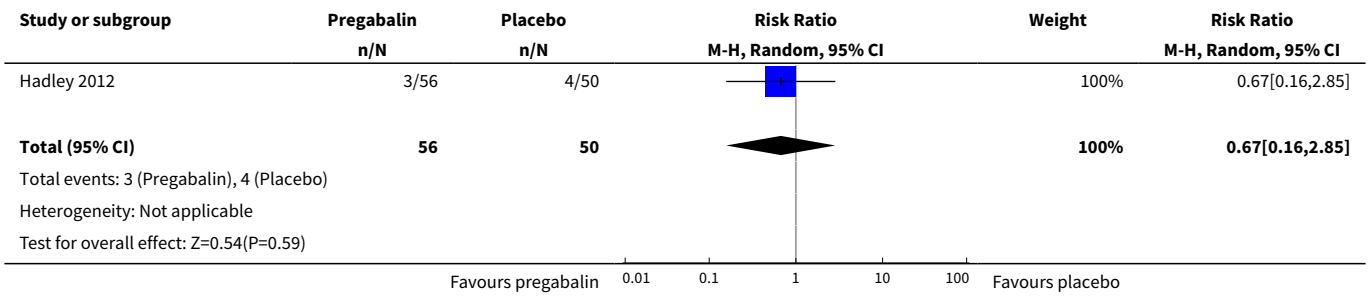
Analysis 4.2. Comparison 4 Pregabalin versus placebo, Outcome 2 Benzodiazepine withdrawal symptoms (Physician Withdrawal Checklist), end of intervention.



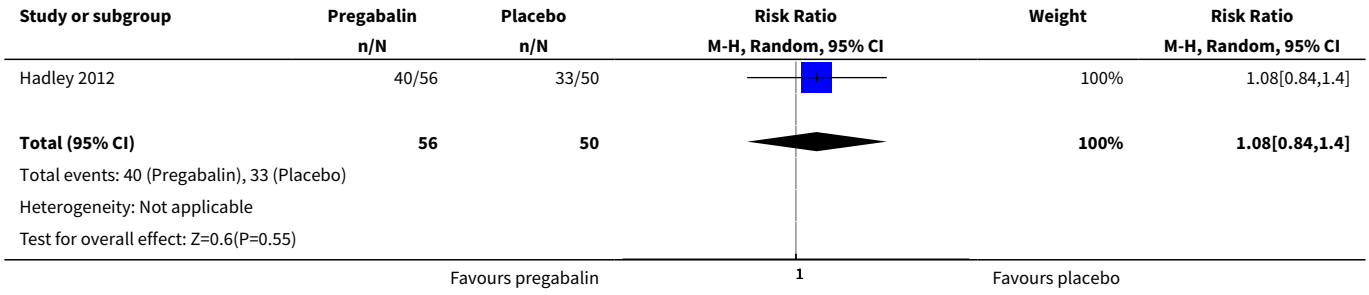
Analysis 4.3. Comparison 4 Pregabalin versus placebo, Outcome 3 Anxiety, HAM-A, end of intervention.



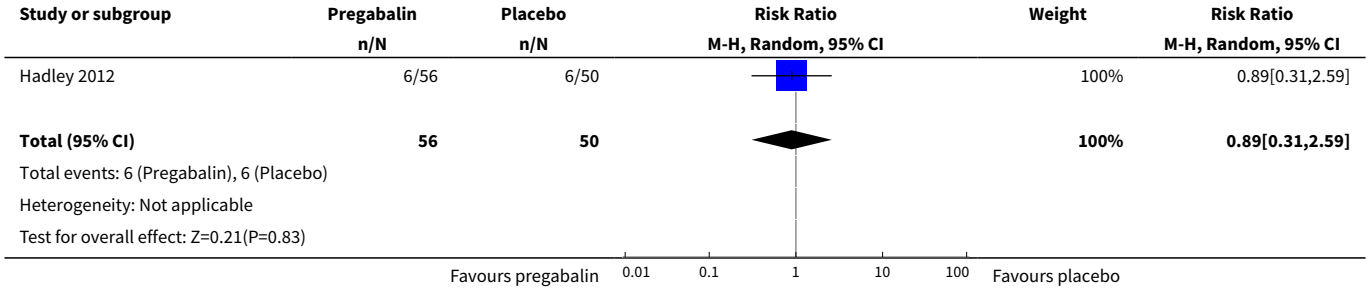
Analysis 4.4. Comparison 4 Pregabalin versus placebo, Outcome 4 Serious adverse events.



Analysis 4.5. Comparison 4 Pregabalin versus placebo, Outcome 5 Non-serious adverse events.



Analysis 4.6. Comparison 4 Pregabalin versus placebo, Outcome 6 Discontinuation due to adverse events.



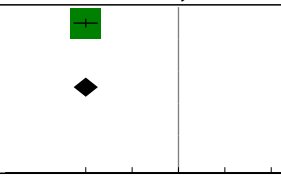
Comparison 5. Captodiame versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Benzodiazepine withdrawal symptoms, BWSQ (Benzodiazepine Withdrawal Symptom Questionnaire), end of intervention	1	81	Mean Difference (IV, Random, 95% CI)	1.00 [-1.13, -0.87]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Anxiety, HAM-A, end of intervention	1	81	Mean Difference (IV, Random, 95% CI)	-5.7 [-6.05, -5.35]
3 Serious adverse events	1	81	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Non-serious adverse events	1	81	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 5.1. Comparison 5 Captodiame versus placebo, Outcome 1 Benzodiazepine withdrawal symptoms, BWSQ (Benzodiazepine Withdrawal Symptom Questionnaire), end of intervention.

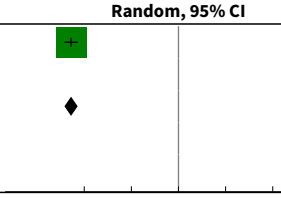
Study or subgroup	Captodiamine N	Captodiamine Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Mercier-Guyon 2004	40	1.3 (0.3)	41	2.3 (0.3)		100%	-1[-1.13,-0.87]
Total ***	**40**		**41**			**100%**	**-1[-1.13,-0.87]**
Heterogeneity: Not applicable							
Test for overall effect: Z=15(P<0.0001)							



Favours captodiamine — Favours placebo

Analysis 5.2. Comparison 5 Captodiame versus placebo, Outcome 2 Anxiety, HAM-A, end of intervention.

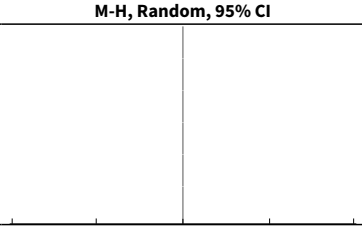
Study or subgroup	Captodiamine N	Captodiamine Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Mercier-Guyon 2004	40	4.7 (0.7)	41	10.4 (0.9)		100%	-5.7[-6.05,-5.35]
Total ***	**40**		**41**			**100%**	**-5.7[-6.05,-5.35]**
Heterogeneity: Not applicable							
Test for overall effect: Z=31.86(P<0.0001)							



Favours captodiamine — Favours placebo

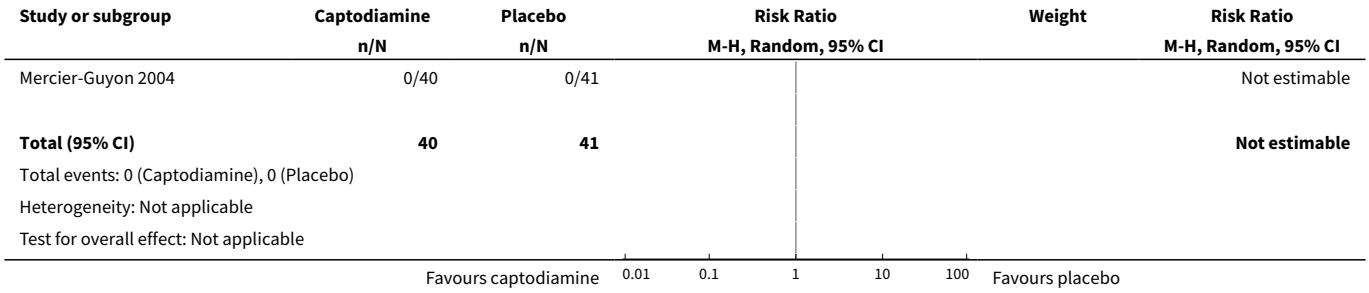
Analysis 5.3. Comparison 5 Captodiame versus placebo, Outcome 3 Serious adverse events.

Study or subgroup	Captodiamine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Mercier-Guyon 2004	0/40	0/41			Not estimable
Total (95% CI)	**40**	**41**			**Not estimable**
Total events: 0 (Captodiamine), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



Favours captodiamine — Favours placebo

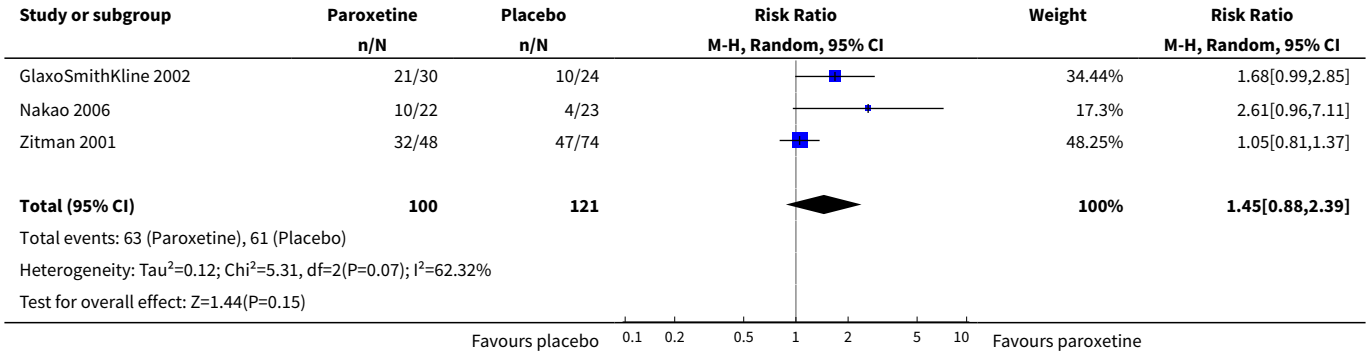
Analysis 5.4. Comparison 5 Captodiame versus placebo, Outcome 4 Non-serious adverse events.



Comparison 6. Paroxetine versus placebo or no intervention

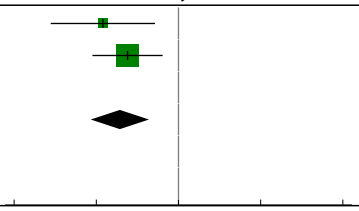
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Benzodiazepine discontinuation, end of intervention	3	221	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.88, 2.39]
2 Benzodiazepine withdrawal symptoms: BWSQ, end of intervention	2	99	Mean Difference (IV, Random, 95% CI)	-3.57 [-5.34, -1.80]
3 Anxiety: HAM-A, end of intervention	2	99	Mean Difference (IV, Random, 95% CI)	-6.75 [-9.64, -3.86]
4 Benzodiazepine withdrawal symptoms: BWSQ, longest follow-up: 6 months	1	54	Mean Difference (IV, Random, 95% CI)	-0.13 [-4.03, 3.77]
5 Serious adverse events	2	176	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Non-serious adverse events	1	54	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.35, 5.03]

Analysis 6.1. Comparison 6 Paroxetine versus placebo or no intervention, Outcome 1 Benzodiazepine discontinuation, end of intervention.



Analysis 6.2. Comparison 6 Paroxetine versus placebo or no intervention, Outcome 2 Benzodiazepine withdrawal symptoms: BWSQ, end of intervention.

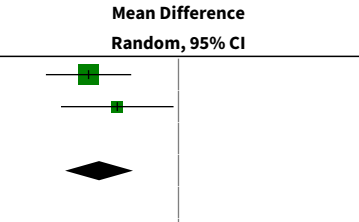
Study or subgroup	Paroxetine N	Paroxetine Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
GlaxoSmithKline 2002	30	-1.8 (4.6)	24	2.8 (6.8)		31.18%	-4.6[-7.77,-1.43]
Nakao 2006	22	-2.7 (3.4)	23	0.4 (3.9)		68.82%	-3.1[-5.24,-0.96]
Total ***	**52**		**47**			**100%**	**-3.57[-5.34,-1.8]**
Heterogeneity: Tau^2=0; Chi^2=0.59, df=1(P=0.44); I^2=0%							
Test for overall effect: Z=3.95(P<0.0001)							



Favours paroxetine — Favours placebo

Analysis 6.3. Comparison 6 Paroxetine versus placebo or no intervention, Outcome 3 Anxiety: HAM-A, end of intervention.

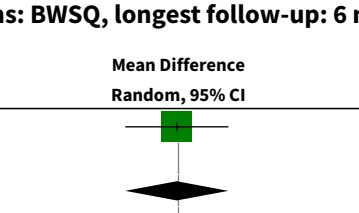
Study or subgroup	Paroxetine N	Paroxetine Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
GlaxoSmithKline 2002	30	-5.4 (6.4)	24	2.3 (7)		63.5%	-7.64[-11.26,-4.02]
Nakao 2006	22	-0.5 (9.7)	23	4.7 (6.2)		36.5%	-5.2[-9.98,-0.42]
Total ***	**52**		**47**			**100%**	**-6.75[-9.64,-3.86]**
Heterogeneity: Tau^2=0; Chi^2=0.64, df=1(P=0.43); I^2=0%							
Test for overall effect: Z=4.58(P<0.0001)							



Favours paroxetine — Favours placebo

Analysis 6.4. Comparison 6 Paroxetine versus placebo or no intervention, Outcome 4 Benzodiazepine withdrawal symptoms: BWSQ, longest follow-up: 6 months.

Study or subgroup	Paroxetine N	Paroxetine Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
GlaxoSmithKline 2002	30	-2.9 (7.8)	24	-2.7 (6.8)		100%	-0.13[-4.03,3.77]
Total ***	**30**		**24**			**100%**	**-0.13[-4.03,3.77]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.07(P=0.95)							

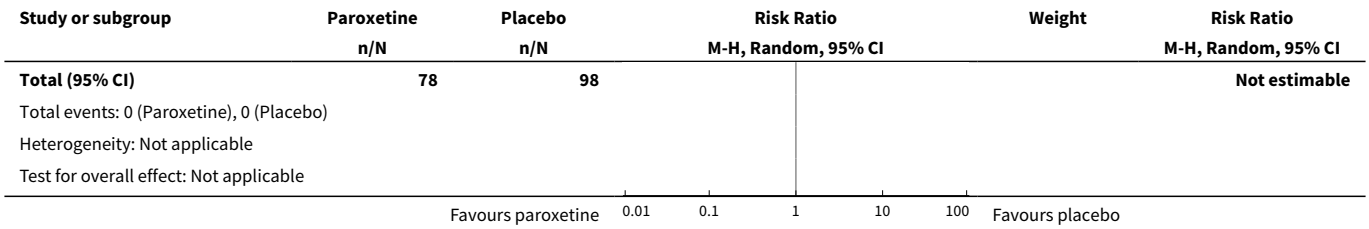


Favours paroxetine — Favours placebo

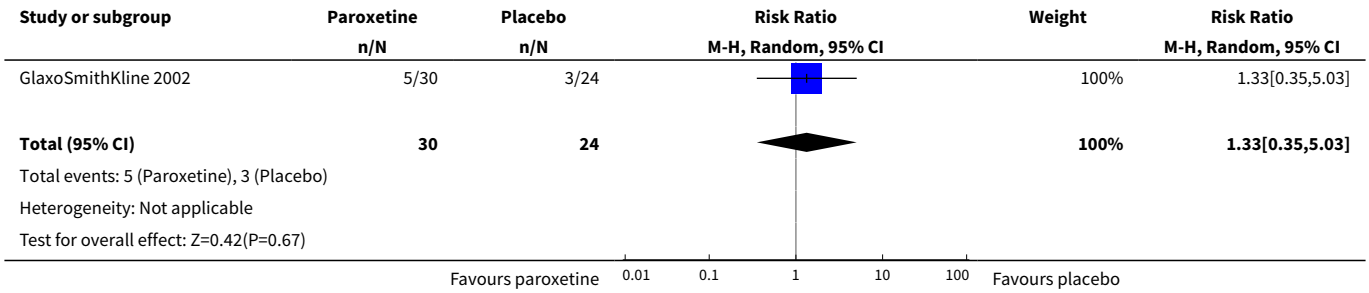
Analysis 6.5. Comparison 6 Paroxetine versus placebo or no intervention, Outcome 5 Serious adverse events.

Study or subgroup	Paroxetine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
GlaxoSmithKline 2002	0/30	0/24			Not estimable
Zitman 2001	0/48	0/74			Not estimable

Favours paroxetine — Favours placebo



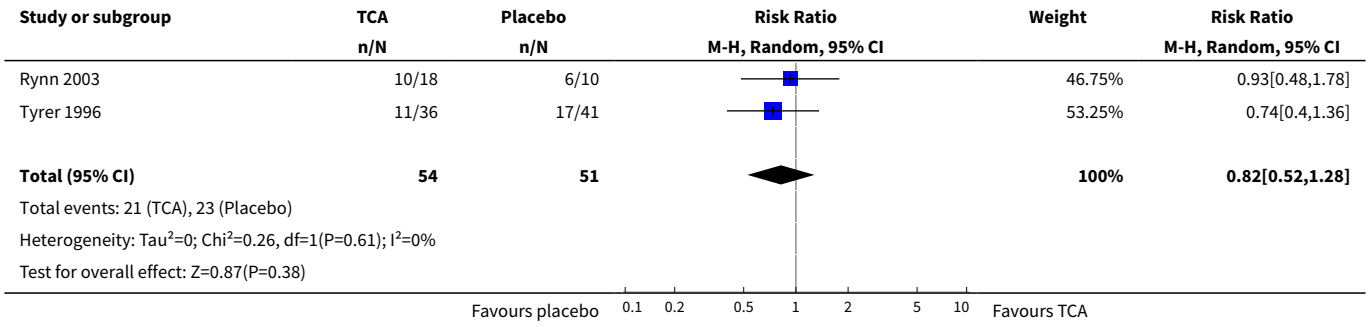
Analysis 6.6. Comparison 6 Paroxetine versus placebo or no intervention, Outcome 6 Non-serious adverse events.



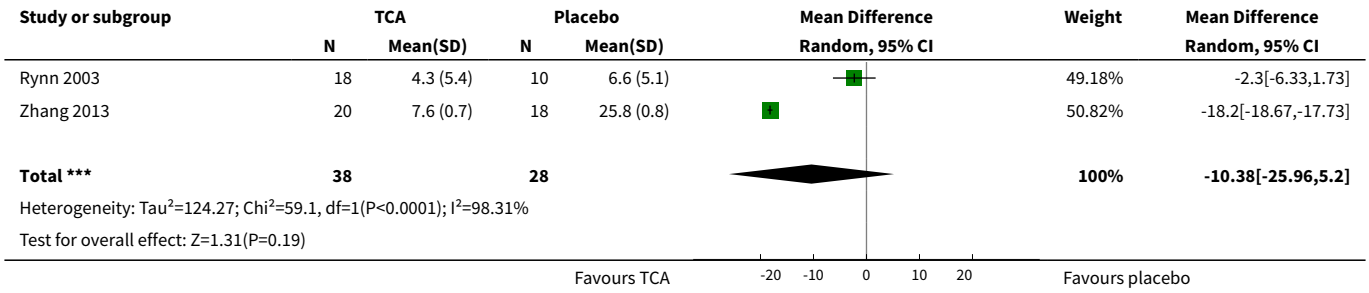
Comparison 7. Tricyclic antidepressants versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Benzodiazepine discontinuation, end of intervention	2	105	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.52, 1.28]
2 Anxiety: HAM-A (change from baseline), end of intervention	2	66	Mean Difference (IV, Random, 95% CI)	-10.38 [-25.96, 5.20]
3 Benzodiazepine discontinuation, longest follow-up	1	47	Risk Ratio (M-H, Random, 95% CI)	2.20 [1.27, 3.82]
4 Benzodiazepine withdrawal symptoms (Physician Withdrawal Checklist), end of intervention	1	38	Mean Difference (IV, Random, 95% CI)	-19.78 [-20.25, -19.31]
5 Relapse to benzodiazepine use, end of intervention	1	36	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.73, 5.47]
6 Discontinuation due to adverse events	2	134	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.42, 3.21]

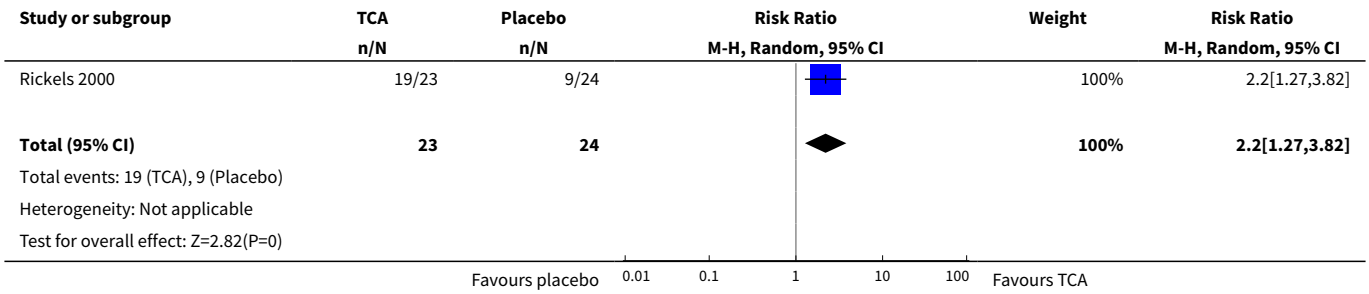
Analysis 7.1. Comparison 7 Tricyclic antidepressants versus placebo, Outcome 1 Benzodiazepine discontinuation, end of intervention.



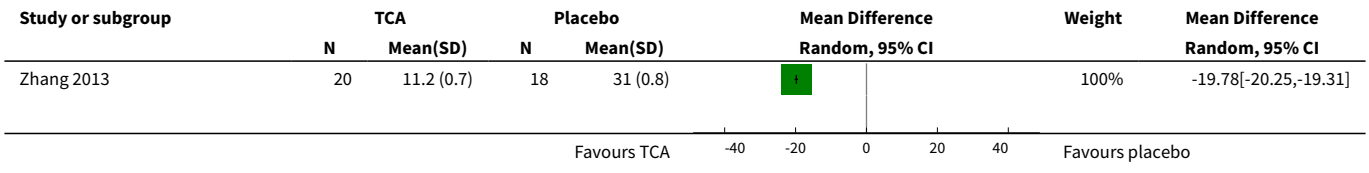
Analysis 7.2. Comparison 7 Tricyclic antidepressants versus placebo, Outcome 2 Anxiety: HAM-A (change from baseline), end of intervention.

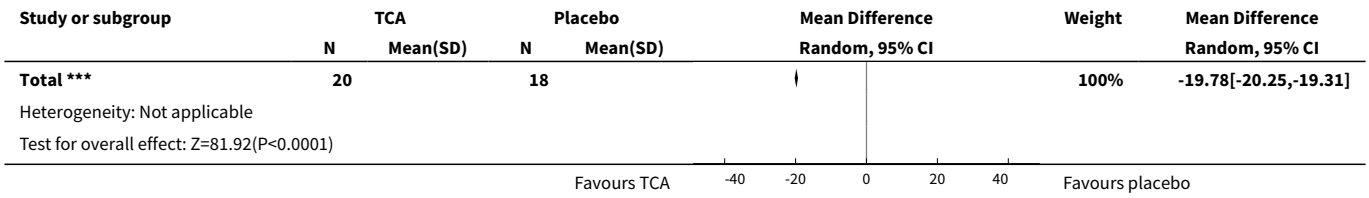


Analysis 7.3. Comparison 7 Tricyclic antidepressants versus placebo, Outcome 3 Benzodiazepine discontinuation, longest follow-up.

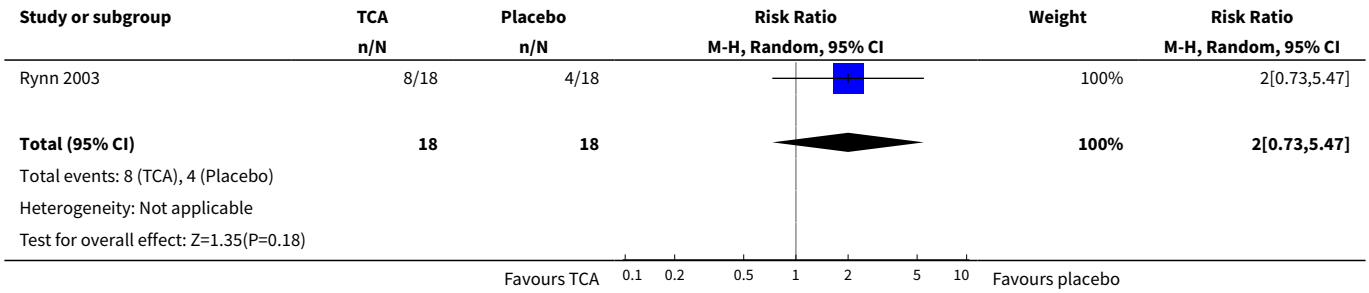


Analysis 7.4. Comparison 7 Tricyclic antidepressants versus placebo, Outcome 4 Benzodiazepine withdrawal symptoms (Physician Withdrawal Checklist), end of intervention.

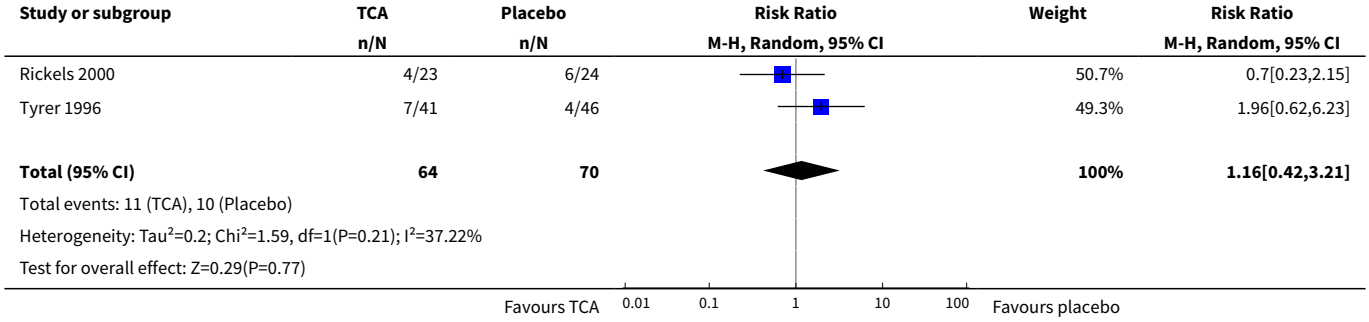




Analysis 7.5. Comparison 7 Tricyclic antidepressants versus placebo, Outcome 5 Relapse to benzodiazepine use, end of intervention.



Analysis 7.6. Comparison 7 Tricyclic antidepressants versus placebo, Outcome 6 Discontinuation due to adverse events.

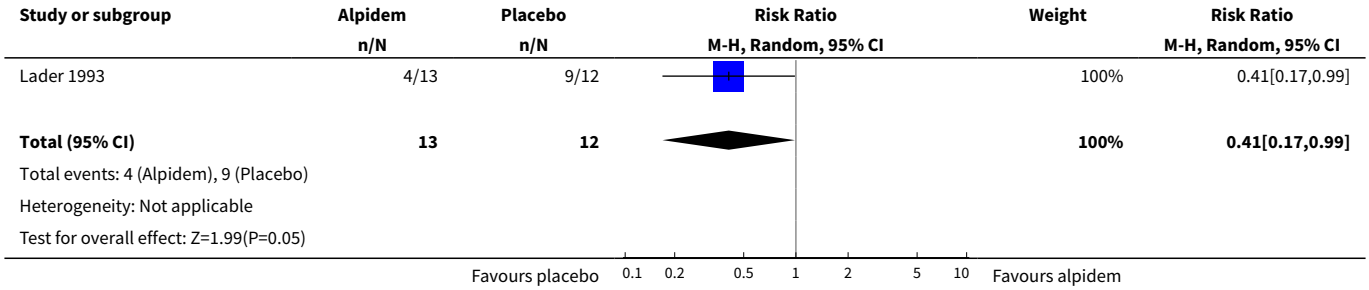


Comparison 8. Alpidem versus placebo

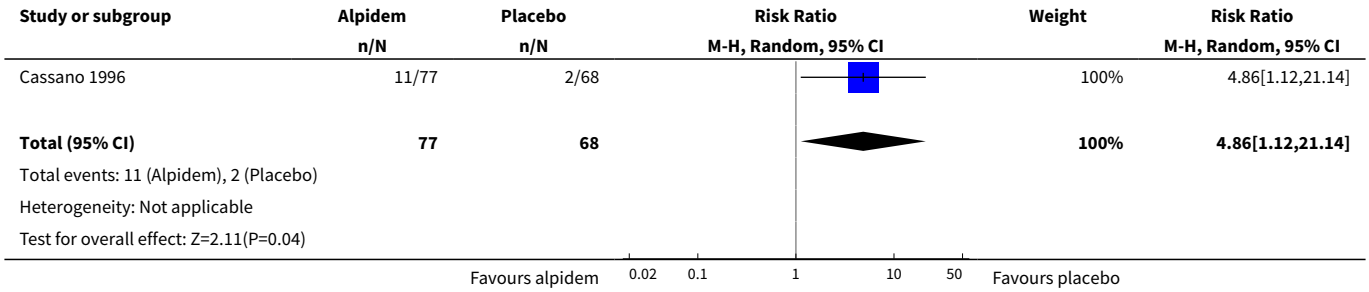
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Benzodiazepine discontinuation, end of intervention	1	25	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.17, 0.99]
2 Withdrawal syndrome (clinical diagnosis), end of intervention	1	145	Risk Ratio (M-H, Random, 95% CI)	4.86 [1.12, 21.14]
3 Anxiety, HAM-A, end of intervention	2	170	Mean Difference (IV, Random, 95% CI)	-1.60 [-4.64, 1.45]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Relapse to benzodiazepine use, end of intervention	1	145	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.09, 1.20]
5 Serious adverse events	1	25	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Discontinuation due to adverse events	1	25	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.05, 4.46]

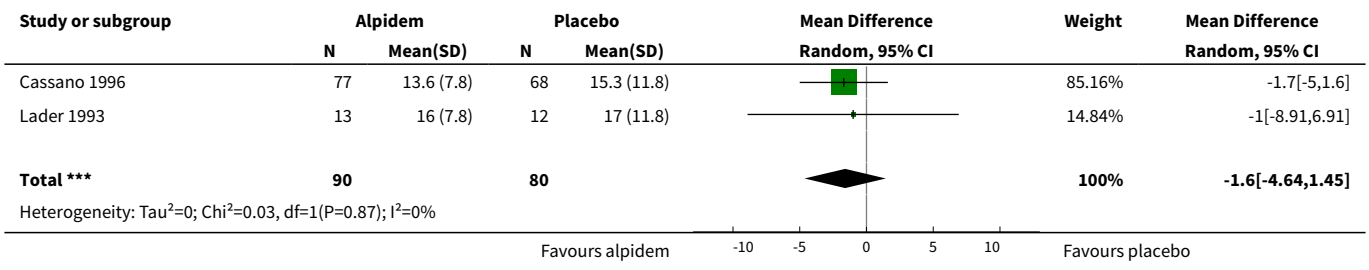
Analysis 8.1. Comparison 8 Alpidem versus placebo, Outcome 1 Benzodiazepine discontinuation, end of intervention.

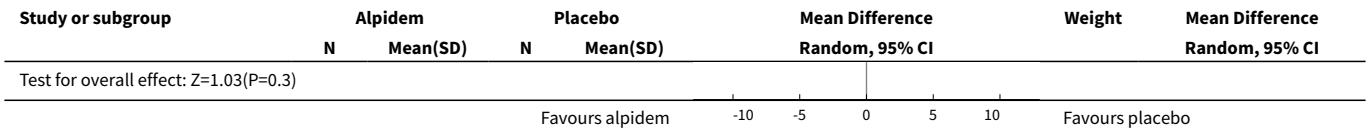


Analysis 8.2. Comparison 8 Alpidem versus placebo, Outcome 2 Withdrawal syndrome (clinical diagnosis), end of intervention.

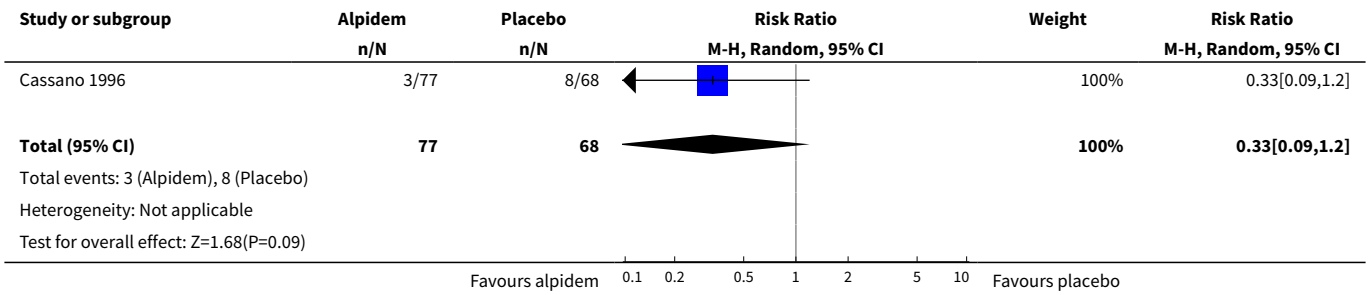


Analysis 8.3. Comparison 8 Alpidem versus placebo, Outcome 3 Anxiety, HAM-A, end of intervention.

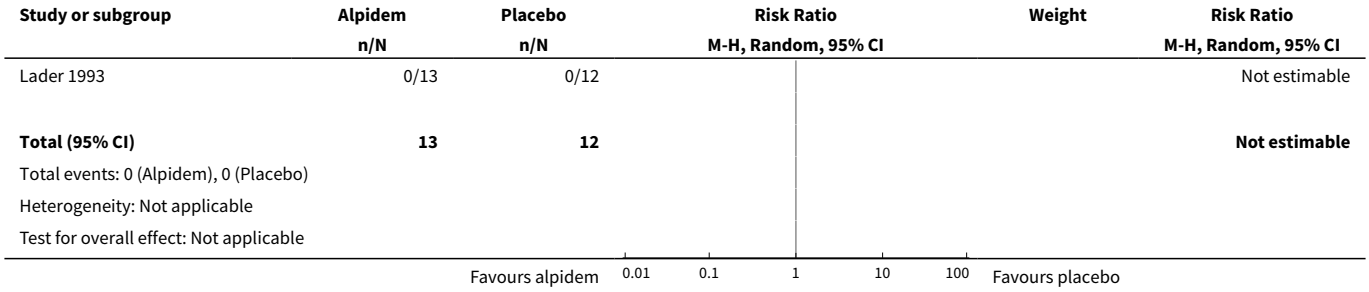




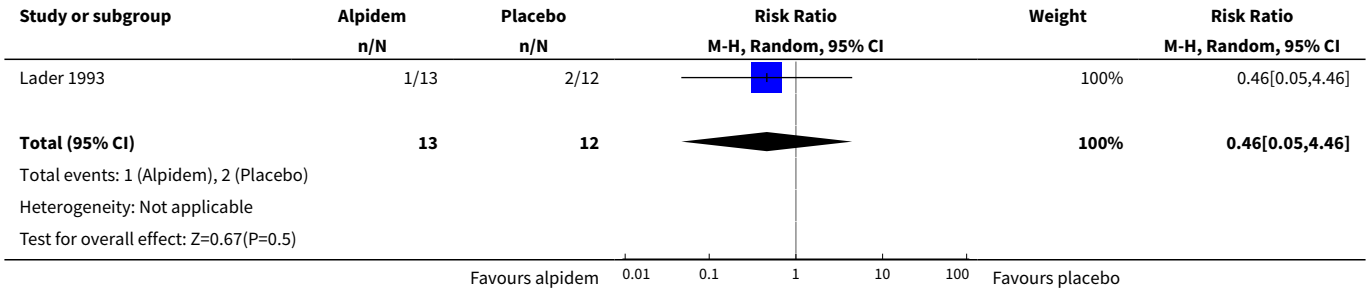
Analysis 8.4. Comparison 8 Alpidem versus placebo, Outcome 4 Relapse to benzodiazepine use, end of intervention.



Analysis 8.5. Comparison 8 Alpidem versus placebo, Outcome 5 Serious adverse events.



Analysis 8.6. Comparison 8 Alpidem versus placebo, Outcome 6 Discontinuation due to adverse events.



Comparison 9. Buspirone versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Benzodiazepine discontinuation, end of intervention	4	143	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.49, 1.37]
2 Anxiety: HAM-A/Hospital Anxiety Depression Scale, end of intervention	2	41	Std. Mean Difference (IV, Random, 95% CI)	0.18 [-0.50, 0.86]
3 Benzodiazepine withdrawal symptoms, end of intervention	1	17	Mean Difference (IV, Random, 95% CI)	4.69 [-14.47, 23.85]
4 Benzodiazepine discontinuation, longest follow-up	1	23	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.34, 1.05]
5 Benzodiazepine withdrawal symptoms, longest follow-up	1	15	Mean Difference (IV, Random, 95% CI)	-1.34 [-14.31, 11.63]
6 Anxiety, Hospital Anxiety Depression Scale, longest follow-up	1	12	Mean Difference (IV, Random, 95% CI)	2.75 [-2.83, 8.33]
7 Discontinuation due to adverse events	1	72	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.92]

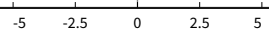
Analysis 9.1. Comparison 9 Buspirone versus placebo, Outcome 1 Benzodiazepine discontinuation, end of intervention.

Study or subgroup	Buspirone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Ashton 1990	4/11	11/12		22.22%	0.4[0.18,0.88]
Lader 1987	5/13	6/11		20.13%	0.71[0.29,1.69]
Morton 1995	6/12	6/12		22.22%	1[0.45,2.23]
Udelman 1990	21/36	17/36		35.44%	1.24[0.79,1.92]
Total (95% CI)	**72**	**71**		**100%**	**0.82[0.49,1.37]**
Total events: 36 (Buspirone), 40 (Placebo)					
Heterogeneity: Tau^2=0.14; Chi^2=6.38, df=3(P=0.09); I^2=52.95%					
Test for overall effect: Z=0.76(P=0.44)					

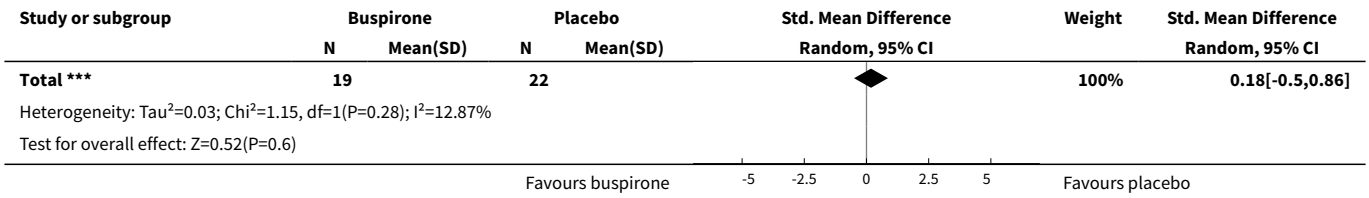
Favours placebo — Favours buspirone

Analysis 9.2. Comparison 9 Buspirone versus placebo, Outcome 2 Anxiety: HAM-A/Hospital Anxiety Depression Scale, end of intervention.

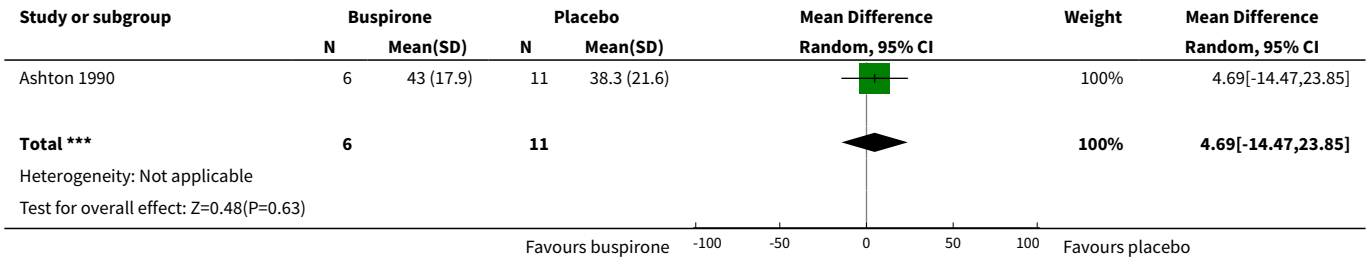
Study or subgroup	Buspirone N	Buspirone Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Ashton 1990	6	15.8 (5)	11	11.9 (6.6)		39.72%	0.61[-0.41,1.63]
Lader 1987	13	22 (21)	11	24 (17)		60.28%	-0.1[-0.9,0.7]



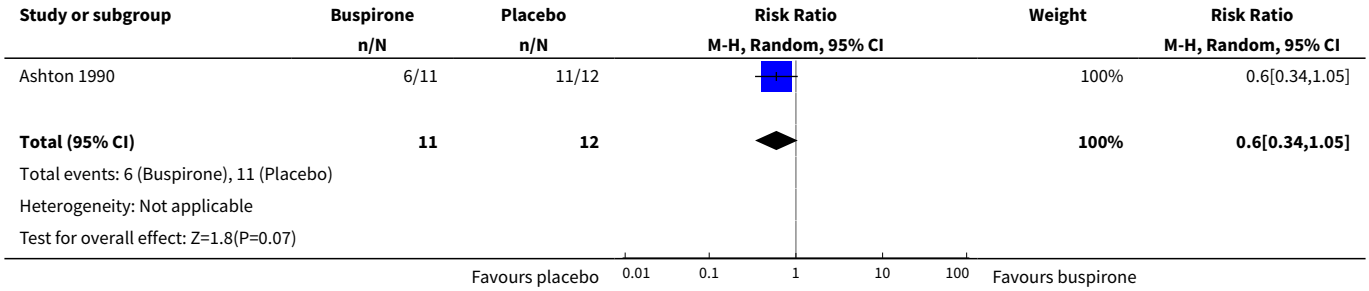
Favours buspirone — Favours placebo



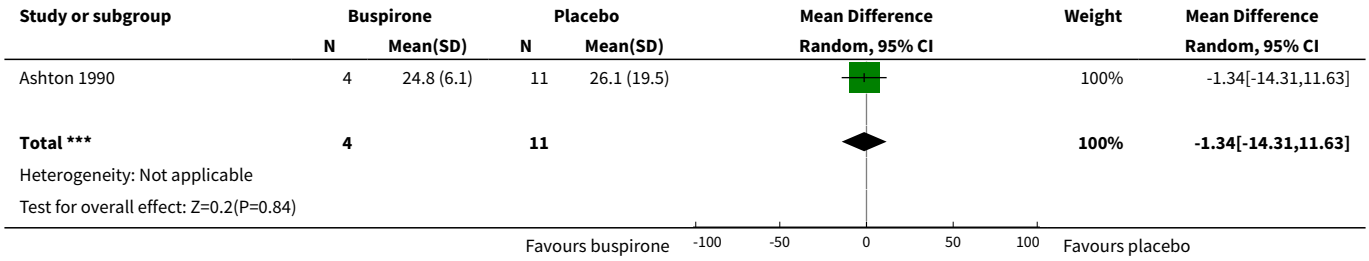
Analysis 9.3. Comparison 9 Buspirone versus placebo, Outcome 3 Benzodiazepine withdrawal symptoms, end of intervention.



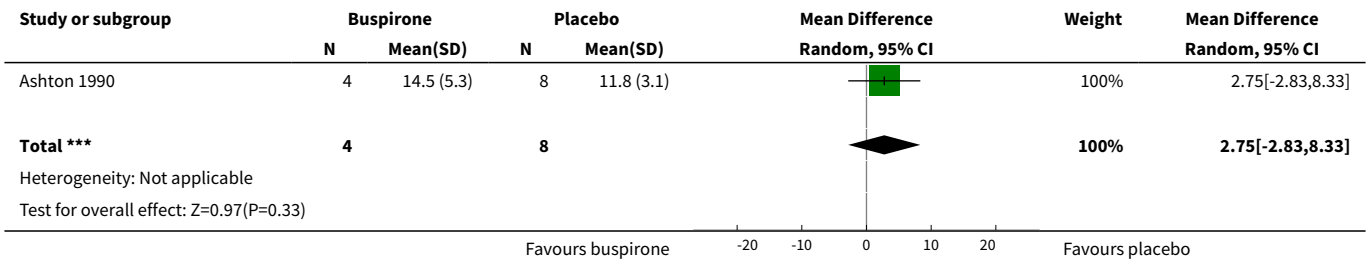
Analysis 9.4. Comparison 9 Buspirone versus placebo, Outcome 4 Benzodiazepine discontinuation, longest follow-up.



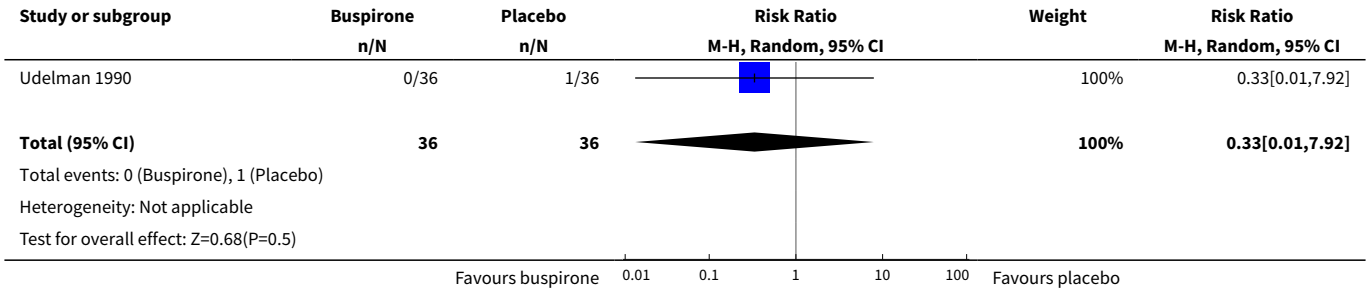
Analysis 9.5. Comparison 9 Buspirone versus placebo, Outcome 5 Benzodiazepine withdrawal symptoms, longest follow-up.



Analysis 9.6. Comparison 9 Buspirone versus placebo, Outcome 6 Anxiety, Hospital Anxiety Depression Scale, longest follow-up.



Analysis 9.7. Comparison 9 Buspirone versus placebo, Outcome 7 Discontinuation due to adverse events.

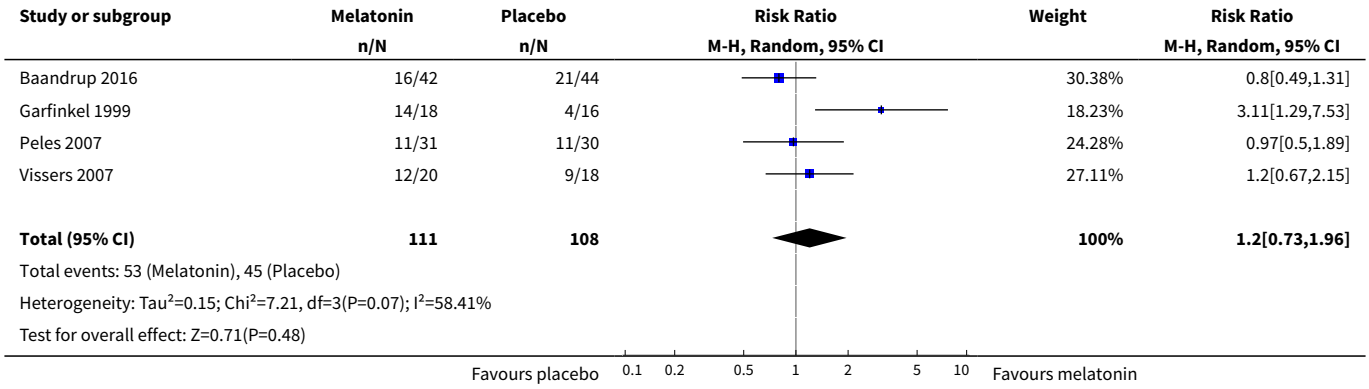


Comparison 10. Melatonin versus placebo

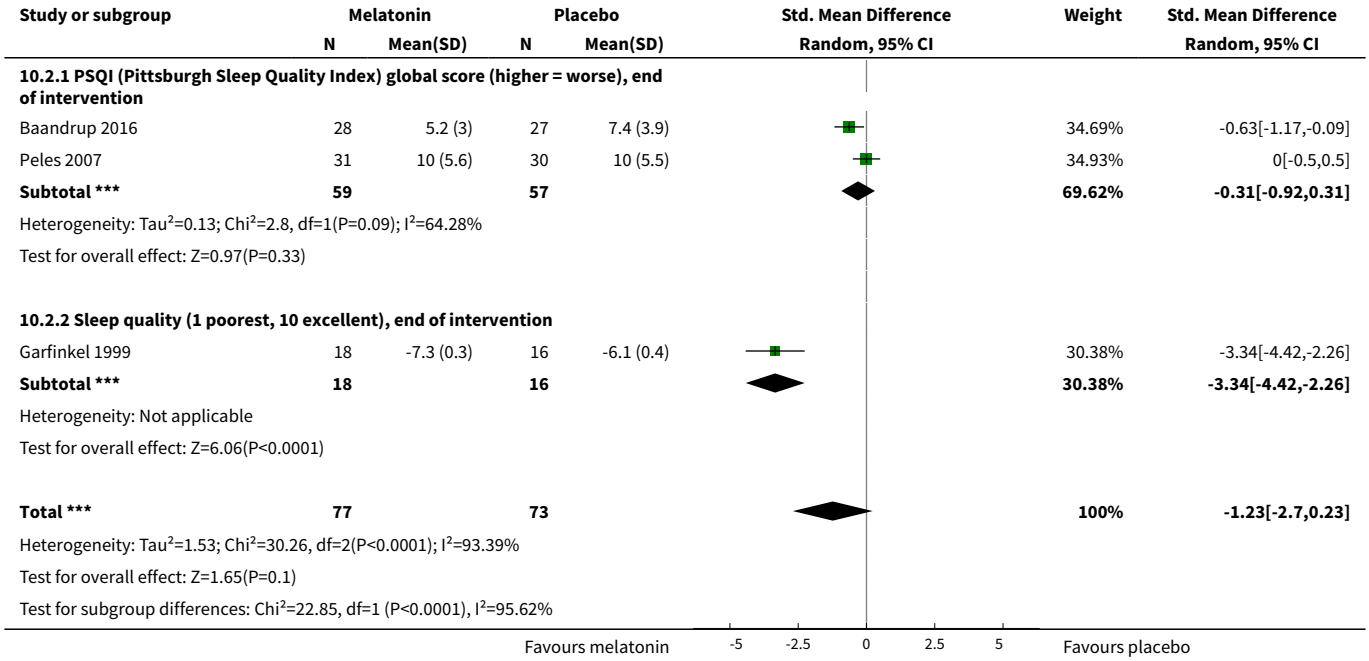
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Benzodiazepine discontinuation, end of intervention	4	219	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.73, 1.96]
2 Insomnia	3	150	Std. Mean Difference (IV, Random, 95% CI)	-1.23 [-2.70, 0.23]
2.1 PSQI (Pittsburgh Sleep Quality Index) global score (higher = worse), end of intervention	2	116	Std. Mean Difference (IV, Random, 95% CI)	-0.31 [-0.92, 0.31]
2.2 Sleep quality (1 poorest, 10 excellent), end of intervention	1	34	Std. Mean Difference (IV, Random, 95% CI)	-3.34 [-4.42, -2.26]
3 Discontinuation due to adverse events	2	120	Risk Ratio (M-H, Random, 95% CI)	2.10 [0.20, 22.26]
4 Benzodiazepine discontinuation, longest follow-up	1	38	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.47, 2.27]
5 Adverse events	1	86	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.52, 1.82]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Relapse to benzodiazepine use, longest follow-up	1	38	Risk Ratio (M-H, Random, 95% CI)	1.8 [0.37, 8.68]

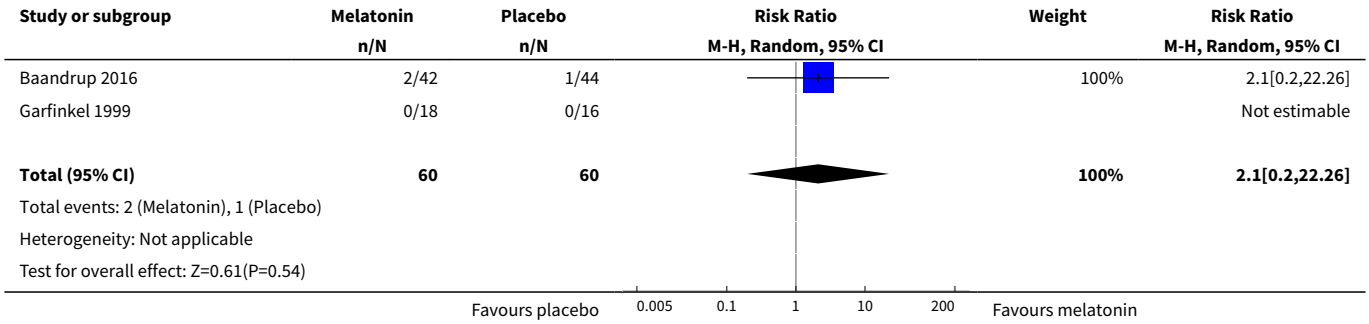
Analysis 10.1. Comparison 10 Melatonin versus placebo, Outcome 1 Benzodiazepine discontinuation, end of intervention.



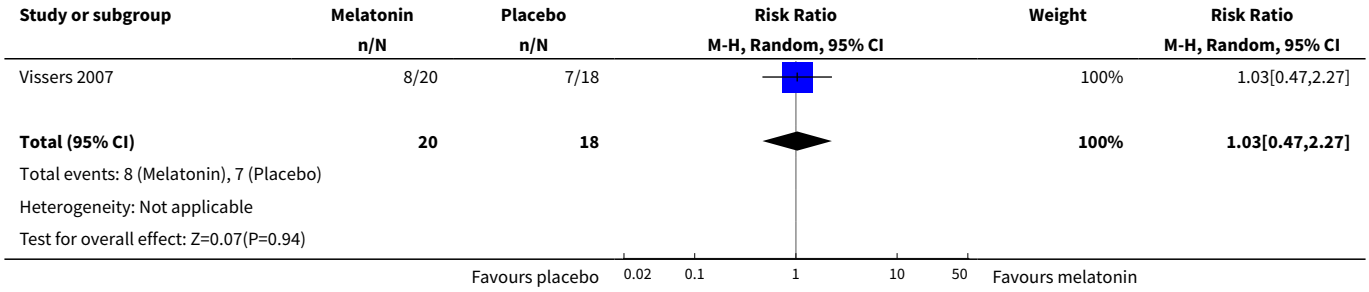
Analysis 10.2. Comparison 10 Melatonin versus placebo, Outcome 2 Insomnia.



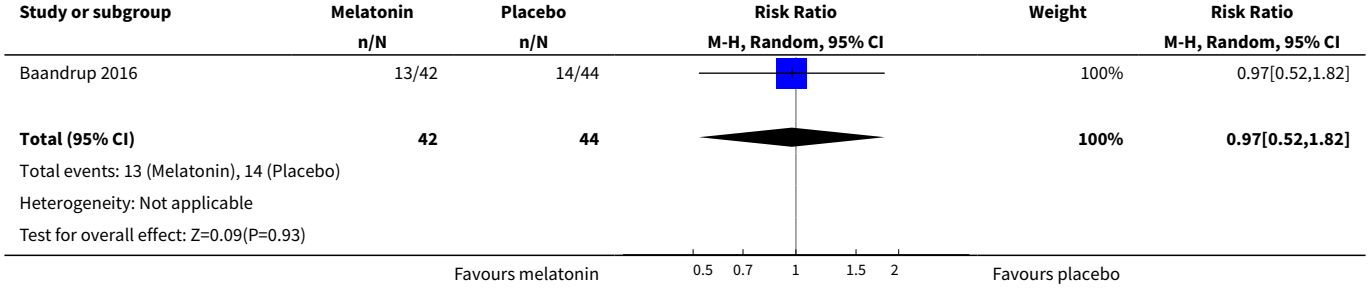
Analysis 10.3. Comparison 10 Melatonin versus placebo, Outcome 3 Discontinuation due to adverse events.



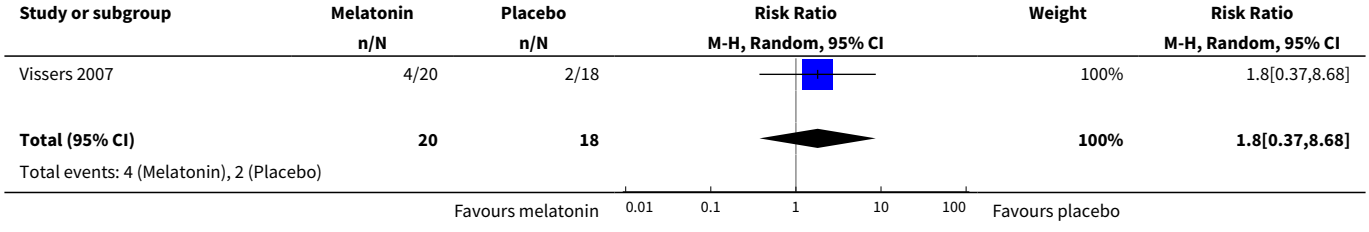
Analysis 10.4. Comparison 10 Melatonin versus placebo, Outcome 4 Benzodiazepine discontinuation, longest follow-up.

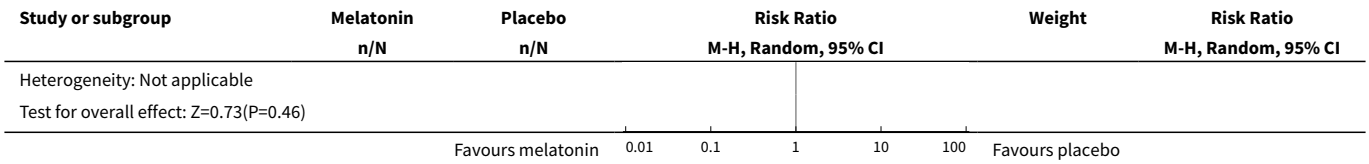


Analysis 10.5. Comparison 10 Melatonin versus placebo, Outcome 5 Adverse events.



Analysis 10.6. Comparison 10 Melatonin versus placebo, Outcome 6 Relapse to benzodiazepine use, longest follow-up.

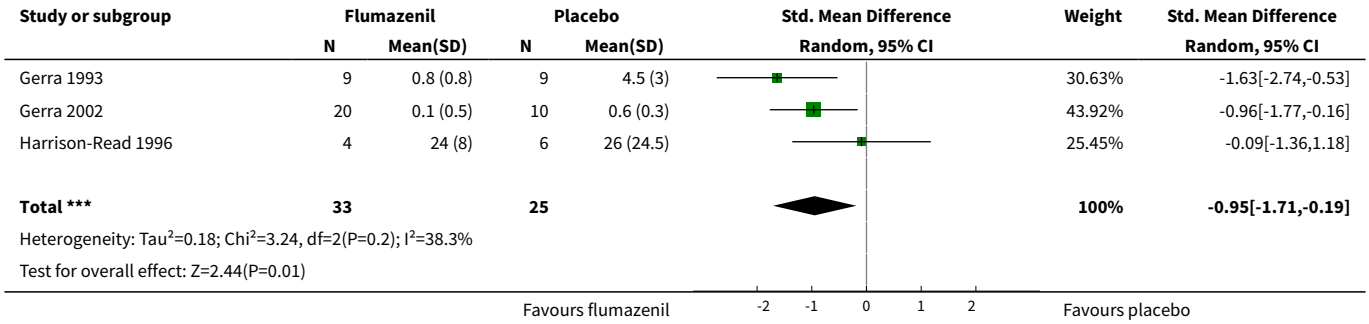




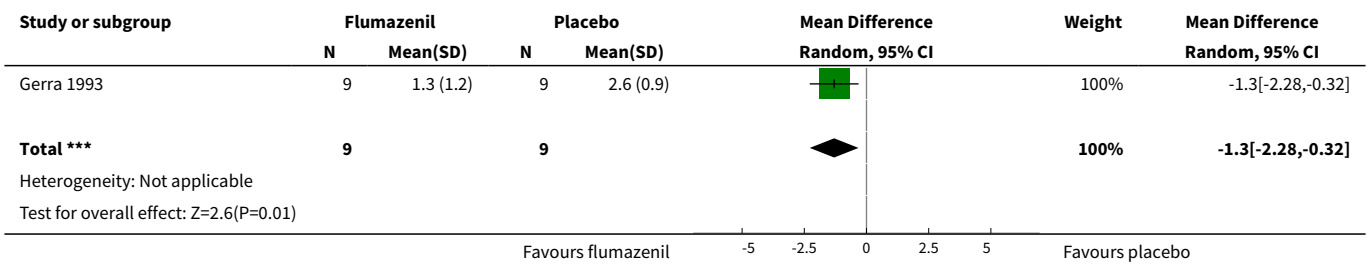
Comparison 11. Flumazenil versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Benzodiazepine withdrawal symptoms, end of intervention	3	58	Std. Mean Difference (IV, Random, 95% CI)	-0.95 [-1.71, -0.19]
2 Anxiety, HAM-D (Hamilton Depression Rating Scale), end of intervention	1	18	Mean Difference (IV, Random, 95% CI)	-1.3 [-2.28, -0.32]
3 Benzodiazepine mean dose, end of intervention	1	10	Mean Difference (IV, Random, 95% CI)	-3.70 [-22.06, 14.66]

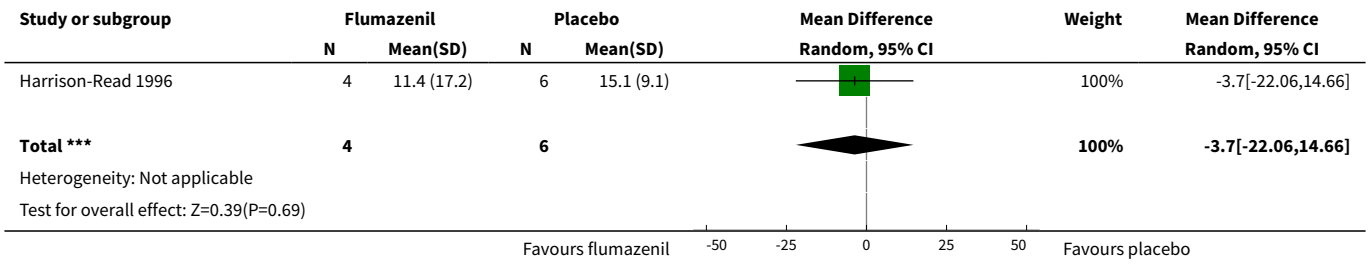
Analysis 11.1. Comparison 11 Flumazenil versus placebo, Outcome 1 Benzodiazepine withdrawal symptoms, end of intervention.



Analysis 11.2. Comparison 11 Flumazenil versus placebo, Outcome 2 Anxiety, HAM-D (Hamilton Depression Rating Scale), end of intervention.



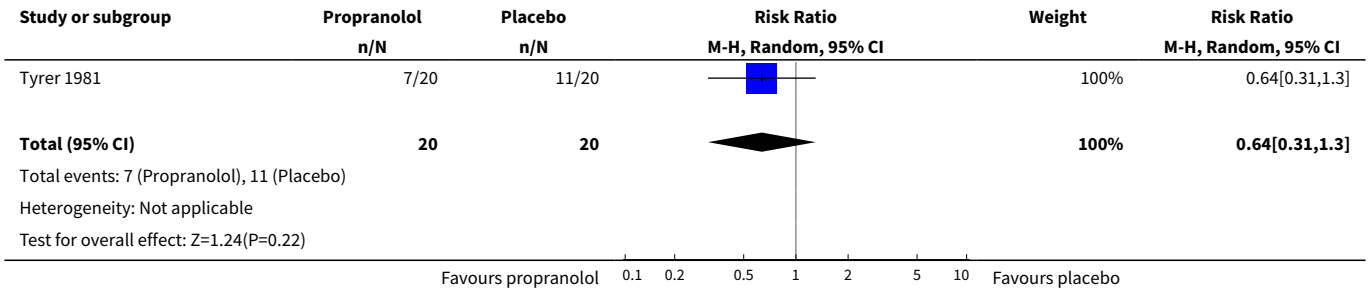
Analysis 11.3. Comparison 11 Flumazenil versus placebo, Outcome 3 Benzodiazepine mean dose, end of intervention.



Comparison 12. Propranolol versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relapse to benzodiazepine use, end of intervention: 2 weeks	1	40	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.31, 1.30]

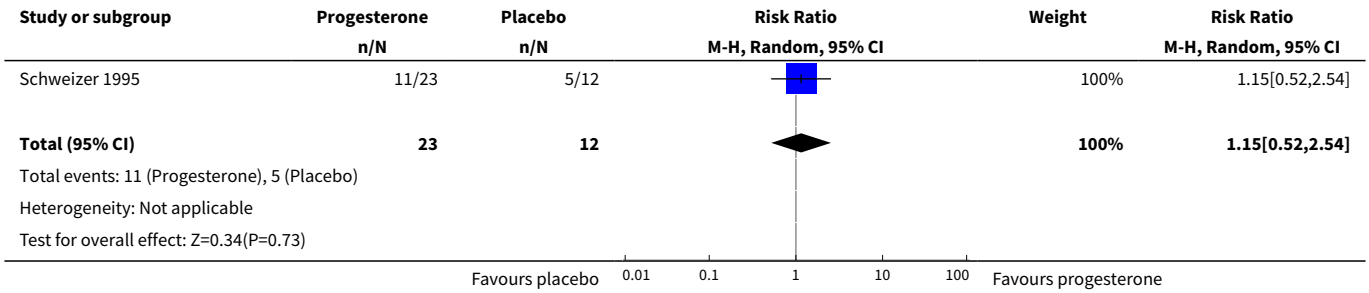
Analysis 12.1. Comparison 12 Propranolol versus placebo, Outcome 1 Relapse to benzodiazepine use, end of intervention: 2 weeks.



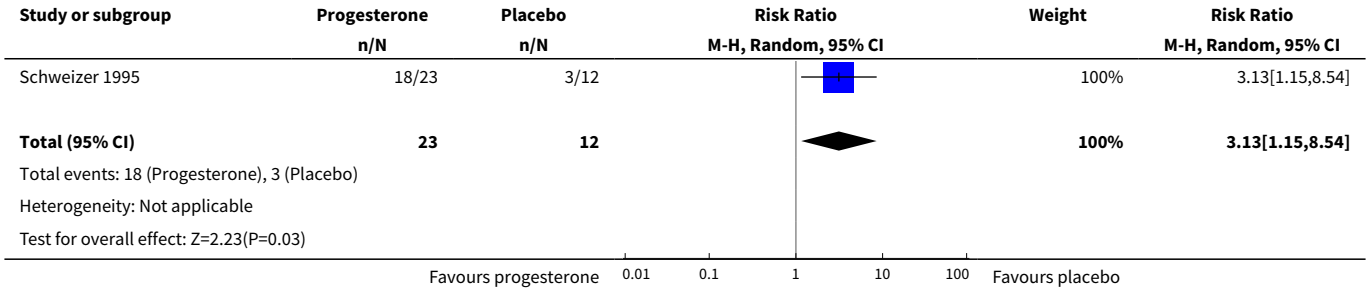
Comparison 13. Progesterone versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Benzodiazepine discontinuation, end of intervention	1	35	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.52, 2.54]
2 Non-serious adverse events	1	35	Risk Ratio (M-H, Random, 95% CI)	3.13 [1.15, 8.54]

Analysis 13.1. Comparison 13 Progesterone versus placebo, Outcome 1 Benzodiazepine discontinuation, end of intervention.



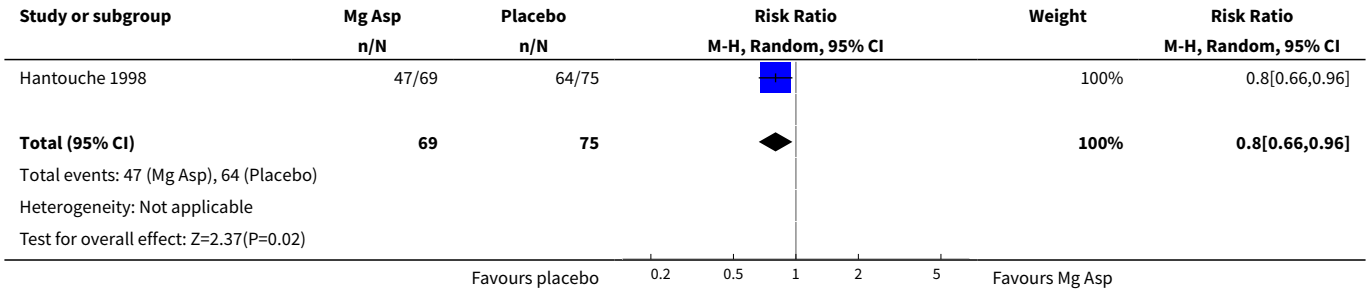
Analysis 13.2. Comparison 13 Progesterone versus placebo, Outcome 2 Non-serious adverse events.



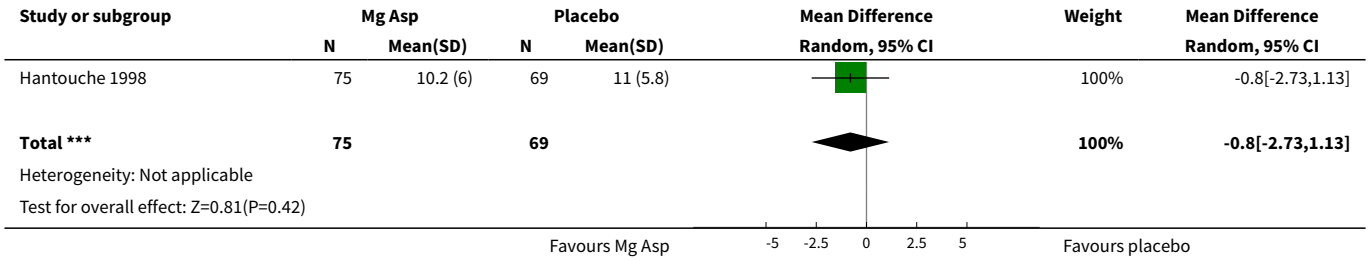
Comparison 14. Magnesium aspartate versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Benzodiazepine discontinuation	1	144	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.66, 0.96]
2 Anxiety	1	144	Mean Difference (IV, Random, 95% CI)	-0.80 [-2.73, 1.13]
3 Relapse to benzodiazepine use	1	144	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.46, 1.87]
4 Non-serious adverse events	1	144	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.18, 1.35]
5 Discontinuation due to adverse events	1	144	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.13, 1.18]

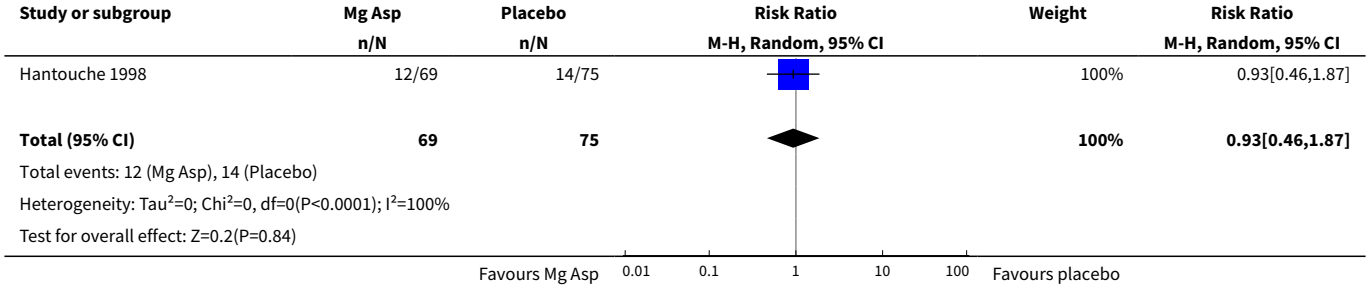
Analysis 14.1. Comparison 14 Magnesium aspartate versus placebo, Outcome 1 Benzodiazepine discontinuation.



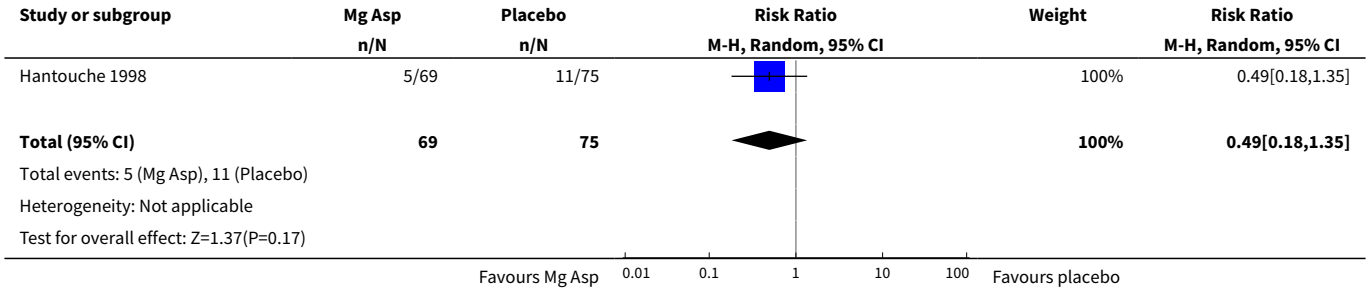
Analysis 14.2. Comparison 14 Magnesium aspartate versus placebo, Outcome 2 Anxiety.



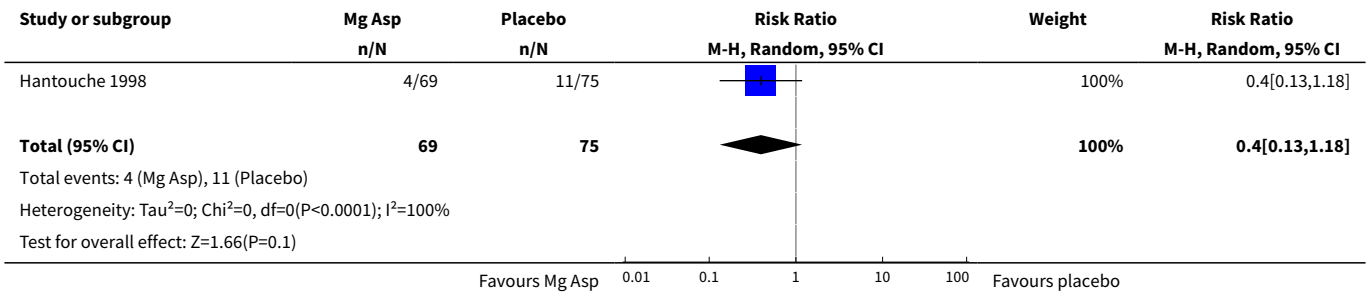
Analysis 14.3. Comparison 14 Magnesium aspartate versus placebo, Outcome 3 Relapse to benzodiazepine use.



Analysis 14.4. Comparison 14 Magnesium aspartate versus placebo, Outcome 4 Non-serious adverse events.



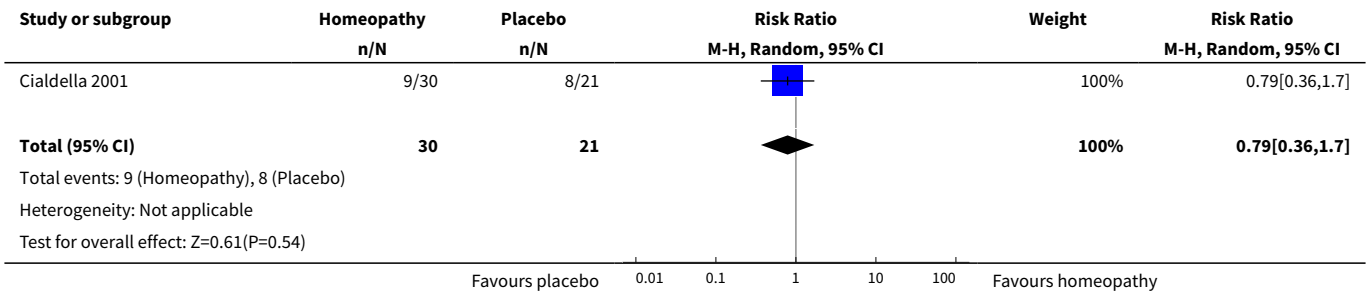
Analysis 14.5. Comparison 14 Magnesium aspartate versus placebo, Outcome 5 Discontinuation due to adverse events.



Comparison 15. Homéogène 46/Sedatif PC (homeopathic drugs) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Benzodiazepine discontinuation	1	51	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.36, 1.70]

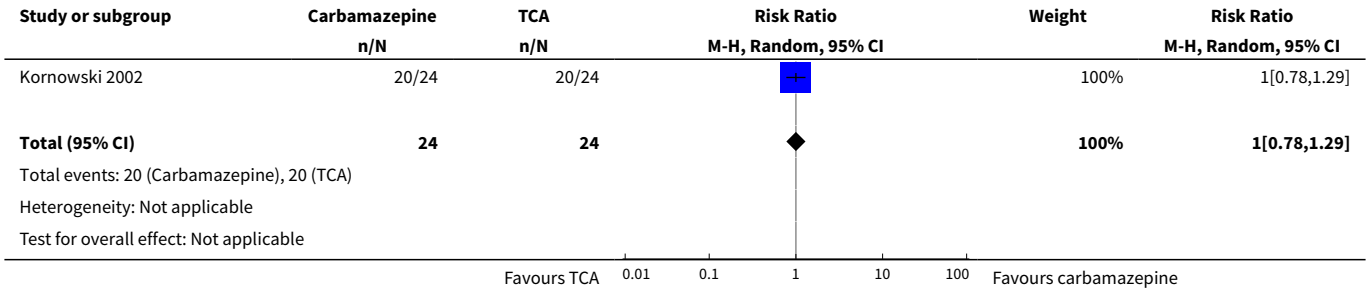
Analysis 15.1. Comparison 15 Homéogène 46/Sedatif PC (homeopathic drugs) versus placebo, Outcome 1 Benzodiazepine discontinuation.



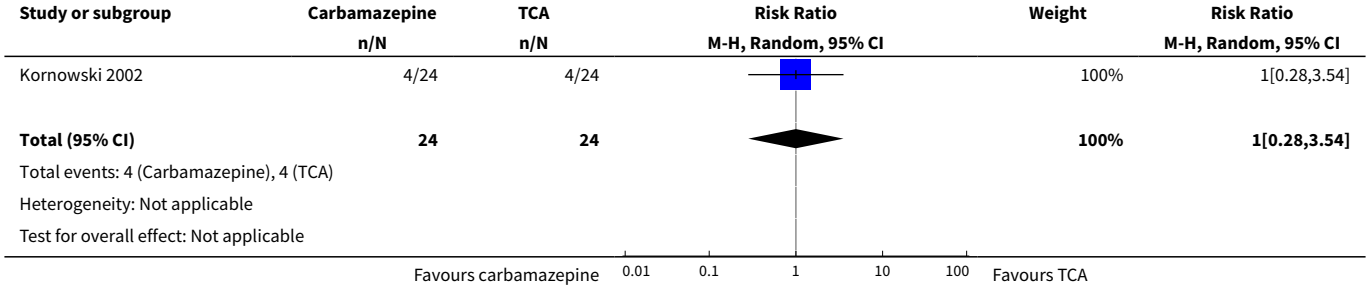
Comparison 16. Carbamazepine versus tricyclic antidepressant

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Benzodiazepine discontinuation, end of intervention	1	48	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.78, 1.29]
2 Relapse to benzodiazepine use	1	48	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.28, 3.54]
3 Serious adverse events	1	48	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

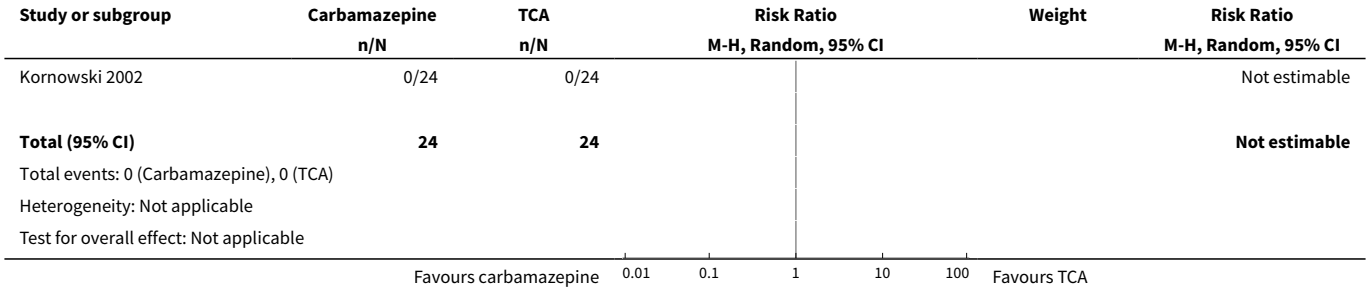
Analysis 16.1. Comparison 16 Carbamazepine versus tricyclic antidepressant, Outcome 1 Benzodiazepine discontinuation, end of intervention.



Analysis 16.2. Comparison 16 Carbamazepine versus tricyclic antidepressant, Outcome 2 Relapse to benzodiazepine use.



Analysis 16.3. Comparison 16 Carbamazepine versus tricyclic antidepressant, Outcome 3 Serious adverse events.

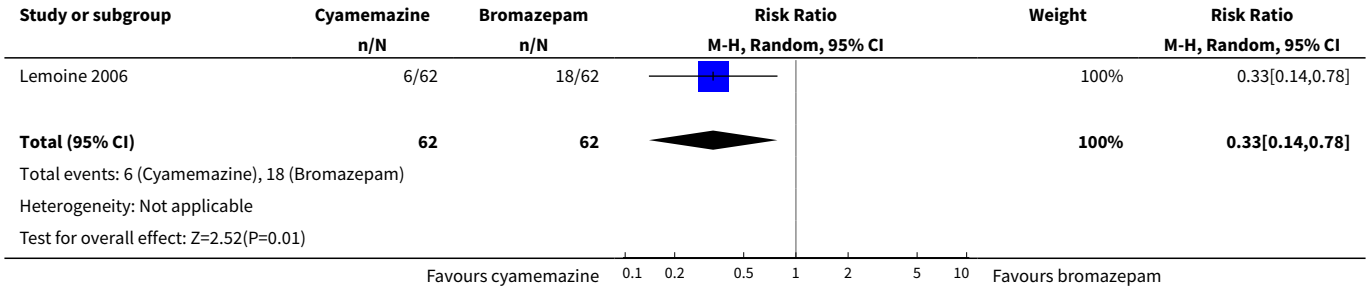


Comparison 17. Cyamemazine versus bromazepam

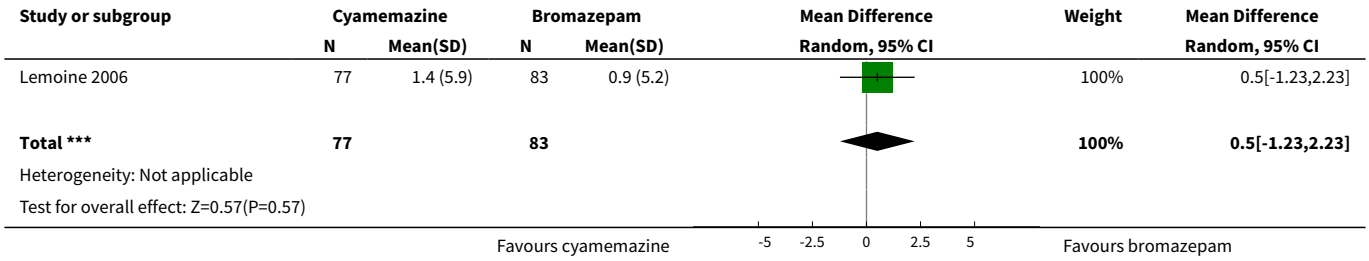
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relapse to benzodiazepine use, longest follow-up	1	124	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.14, 0.78]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Anxiety: Maximum amplitude of rebound (HAM-A), end of intervention	1	160	Mean Difference (IV, Random, 95% CI)	0.50 [-1.23, 2.23]
3 Discontinuation due to adverse events	1	160	Risk Ratio (M-H, Random, 95% CI)	2.87 [0.79, 10.44]
4 Non-serious adverse events	1	160	Risk Ratio (M-H, Random, 95% CI)	1.68 [1.01, 2.78]

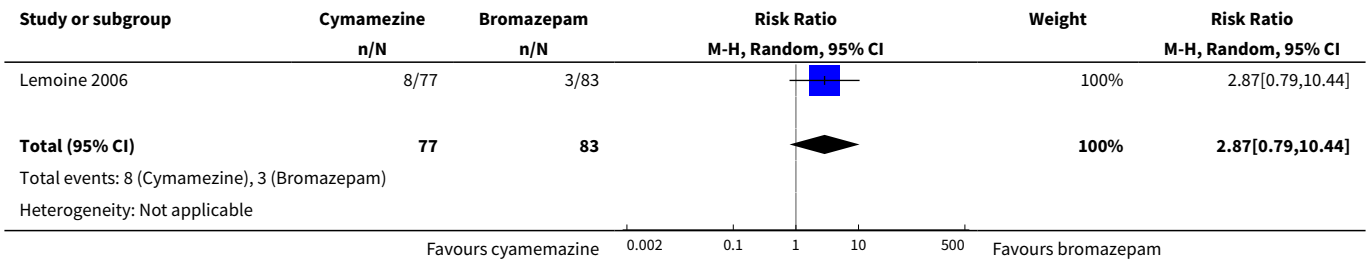
Analysis 17.1. Comparison 17 Cyamemazine versus bromazepam, Outcome 1 Relapse to benzodiazepine use, longest follow-up.

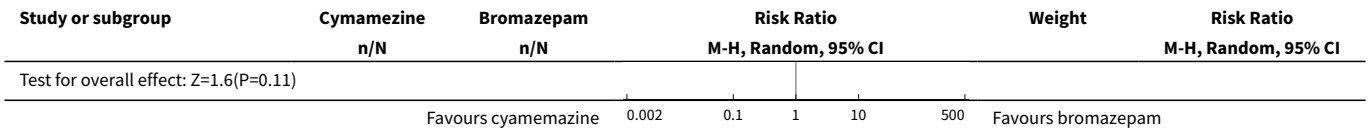


Analysis 17.2. Comparison 17 Cyamemazine versus bromazepam, Outcome 2 Anxiety: Maximum amplitude of rebound (HAM-A), end of intervention.

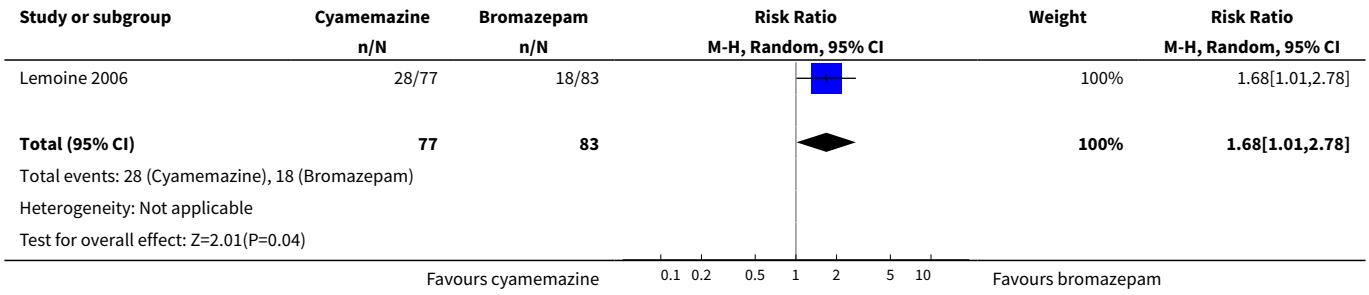


Analysis 17.3. Comparison 17 Cyamemazine versus bromazepam, Outcome 3 Discontinuation due to adverse events.





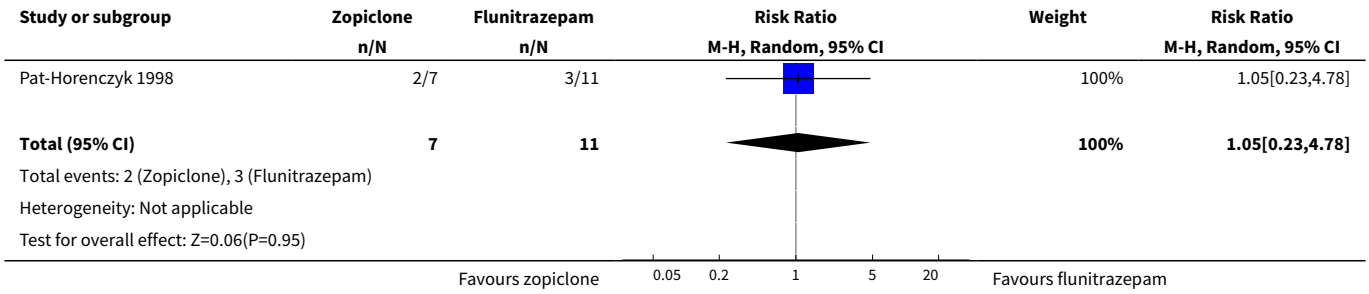
Analysis 17.4. Comparison 17 Cyamemazine versus bromazepam, Outcome 4 Non-serious adverse events.



Comparison 18. Zopiclone versus flunitrazepam

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relapse to benzodiazepine use, longest follow-up	1	18	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.23, 4.78]

Analysis 18.1. Comparison 18 Zopiclone versus flunitrazepam, Outcome 1 Relapse to benzodiazepine use, longest follow-up.



APPENDICES

Appendix 1. Search strategy for Cochrane Drugs and Alcohol Group's Specialised Register of Trials

1. ((benzodiazepine*):xdi) AND (INREGISTER)

2. ((((benzodiazepine* OR chlordiazepoxide OR diazepam OR alprazolam OR lorazepam OR prazepam OR clobazam OR bromazepam OR flurazepam OR triazolam OR clonazepam OR temazepam OR nitrazepam OR lormetazepam OR flunitrazepam OR oxazepam OR zopiclone

OR zolpidem OR zaleplone OR eszopiclone) NEAR3 (abuse* OR abusing OR addict* OR chronic OR dependen* OR 'long-term' OR 'misus* OR overuse)))) AND (INREGISTER)

3. #1 OR #2

4. (((abstinen* OR abstain* OR cessat* OR detox* OR discontinu* OR reduce* OR reducing OR reduct* OR stop* OR taper* OR withdraw* OR substitut*))) AND (INREGISTER)

5. #3 AND #4

Appendix 2. Search strategy for the Cochrane Central Register of Controlled Trials (CENTRAL)

1. MeSH descriptor: [Substance-Related Disorders] this term only

2. (benzodiazepine* near (abuse* or abusing or addict* or chronic or dependen* or 'long-term' or 'misus* or overuse)):ti,ab,kw (Word variations have been searched)

3. MeSH descriptor: [Substance Withdrawal Syndrome] this term only

4. #1 or #2 or #3

5. (benzodiazepine* or BZD or chlordiazepoxide or diazepam or alprazolam or lorazepam or prazepam or clobazam or bromazepam or flurazepam or triazolam or clonazepam or temazepam or nitrazepam or lormetazepam or flunitrazepam or oxazepam or zopiclone or zolpidem or zaleplone or eszopiclone):ti,ab,kw (Word variations have been searched)

6. MeSH descriptor: [Benzodiazepines] explode all trees

7. #5 or #6

8. (abstinen* or abstain* or cessat* or detox* or discontinu* or reduce* or reducing or reduct* or stop* or taper* or withdraw* or substitut*):ti,ab,kw (Word variations have been searched)

9. #4 and #7 and #8 in Trials

Appendix 3. PubMed search strategy

1. "Substance-Related Disorders"[Mesh]

2. abuse*[tiab] OR abusing[tiab] OR addict*[tiab] OR chronic[tiab] OR dependen*[tiab] OR “long-term”[tiab] OR misus*[tiab] OR overuse[tiab]

3. "Substance Withdrawal Syndrome"[Mesh]

4. #1 OR #2 OR #3

5. "Benzodiazepines"[Mesh]

6. Benzodiazepine*[tiab] OR BZD[tiab] OR chlordiazepoxide[tiab] OR diazepam[tiab] OR alprazolam[tiab] OR lorazepam[tiab] OR prazepam[tiab] OR clobazam[tiab] OR bromazepam[tiab] OR flurazepam[tiab] OR triazolam[tiab] OR clonazepam[tiab] OR temazepam[tiab] OR nitrazepam[tiab] OR lormetazepam[tiab] OR flunitrazepam[tiab] OR oxazepam[tiab] or zopiclone[tiab] OR zolpidem[tiab] OR zaleplone[tiab] OR eszopiclone[tiab]

7. #5 OR #6

8. abstinen*[tiab] OR abstain*[tiab] OR cessat*[tiab] OR detox*[tiab] OR discontinu*[tiab] OR reduce*[tiab] OR reducing[tiab] OR reduct* [tiab] OR stop*[tiab] OR taper*[tiab] OR withdraw*[tiab] OR substitut*[tiab]

9. randomised controlled trial [pt]

10. controlled clinical trial [pt]

11. randomised [tiab]

12. placebo [tiab]

13. clinical trials as topic [mesh: noexp]

14. randomly [tiab]

15. trial [ti]

16. #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15

17. animals [mh] NOT humans [mh]

18. #16 NOT #17

19. #4 AND #7 AND #8 AND #18

Appendix 4. Search strategy for Embase

1. substance abuse'/exp OR 'drug dependence'/exp

2. (benzodiazepine* NEAR/6 (abuse* OR abusing OR addict* OR chronic OR dependen* OR 'long-term' OR 'misus* OR overuse)):ab,ti

3. withdrawal syndrome'/exp

4. #1 OR #2 OR #3

5. benzodiazepine derivative'/exp

6. enzodiazepine*:ab,ti OR BZD:ab,ti OR chlordiazepoxide:ab,ti OR diazepam:ab,ti OR alprazolam:ab,ti OR lorazepam:ab,ti OR prazepam:ab,ti OR clobazam:ab,ti OR bromazepam:ab,ti OR flurazepam:ab,ti OR triazolam:ab,ti OR clonazepam:ab,ti OR temazepam:ab,ti OR nitrazepam:ab,ti OR lormetazepam:ab,ti OR flunitrazepam:ab,ti OR oxazepam:ab,ti OR zopiclone:ab,ti OR zolpidem:ab,ti OR zaleplone:ab,ti OR eszopiclone:ab,ti

7. #5 OR #6

8. abstinen*:ab,ti OR abstain*:ab,ti OR cessat*:ab,ti OR detox*:ab,ti OR discontinu*:ab,ti OR reduce*:ab,ti OR reducing:ab,ti OR reduct* :ab,ti OR stop*:ab,ti OR taper*:ab,ti OR withdraw*:ab,ti OR substitut*:ab,ti

9. #4 AND #7 AND #8

10. 'randomised controlled trial'/exp

11. 'single blind procedure'/exp

12. 'double blind procedure'/exp

13. 'crossover procedure'/exp

14. #10 OR #11 OR #12 OR #13

15. random*:ab,ti

16. placebo*:ab,ti

17. allocat*:ab,ti

18. crossover*:ab,ti

19. 'cross over':ab,ti

20. trial:ti

21. (doubl* NEXT/1 blind*):ab,ti

22. #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21

23. #14 OR #22

24. 'animal'/de

25. 'animal experiment'/de

26. nonhuman'/de

27. #24 OR #25 OR #26

28. 'human'/de

29. #27 AND #28

30. #27 NOT #29

31. #23 NOT #30

32. #9 AND #31

Appendix 5. Search strategy for CINAHL

1. (MH "Substance Use Disorders+")

2. TX (benzodiazepine* N6 (abuse* or abusing or addict* or chronic or dependen* or 'long-term' or 'misus* or overuse))

3. TI ((benzodiazepine* N6 (abuse* or abusing or addict* or chronic or dependen* or 'long-term' or 'misus* or overuse))) OR AB ((benzodiazepine* N6 (abuse* or abusing or addict* or chronic or dependen* or 'long-term' or 'misus* or overuse)))

4. (MH "Substance Withdrawal Syndrome+")

5. S1 OR S2 OR S3 OR S4

6. TI (benzodiazepine* or BZD or chlordiazepoxide or diazepam or alprazolam or lorazepam or prazepam or clobazam or bromazepam or flurazepam or triazolam or clonazepam or temazepam or nitrazepam or lormetazepam or flunitrazepam or oxazepam or zopiclone or zolpidem or zaleplone or eszopiclone) OR AB (benzodiazepine* or BZD or chlordiazepoxide or diazepam or alprazolam or lorazepam or prazepam or clobazam or bromazepam or flurazepam or triazolam or clonazepam or temazepam or nitrazepam or lormetazepam or flunitrazepam or oxazepam or zopiclone or zolpidem or zaleplone or eszopiclone)

7. (MH "Antianxiety Agents, Benzodiazepine+")

8. S6 OR S7

9. TX (abstinen* or abstain* or cessat* or detox* or discontinu* or reduce* or reducing or reduct* or stop* or taper* or withdraw* or substitut*)

10. S5 AND S8 AND S9

11. MH "Clinical Trials+"

12. PT Clinical trial

13. TI clinic* N1 trial* or AB clinic* N1 trial*

14. TI (singl* or doubl* or trebl* or tripl*) and TI (blind* or mask*)

15. AB (singl* or doubl* or trebl* or tripl*) and AB (blind* or mask*)

16. TI randomi?ed control* trial* or AB randomi?ed control* trial*

17. MH "Random Assignment"

18. TI random* allocat* or AB random* allocat*

19. MH "Placebos"

20. TI placebo* or AB placebo*

21. MH "Quantitative Studies"

22. S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21

23. S10 AND S22

24. S10 AND S22Exclude MEDLINE records

Appendix 6. Search strategy for Web of Science

1. TS=((benzodiazepine* OR chlordiazepoxide OR diazepam OR alprazolam OR lorazepam OR prazepam OR clobazam OR bromazepam OR flurazepam OR triazolam OR clonazepam OR temazepam OR nitrazepam OR lormetazepam OR flunitrazepam OR oxazepam OR zopiclone OR zolpidem OR zaleplone OR eszopiclone) NEAR/6 (abuse* OR abusing OR addict* OR chronic OR dependen* OR 'long-term' OR 'misus* OR overuse))

2. TOPIC: (abstinen* OR abstain* OR cessat* OR detox* OR discontinu* OR reduce* OR reducing OR reduct* OR stop* OR taper* OR withdraw* OR substitut*)

3. #2 AND #1

4. TS= clinical trial* OR TS=research design OR TS=comparative stud* OR TS=evaluation stud* OR TS=controlled trial* OR TS=follow-up stud* OR TS=prospective stud* OR TS=random* OR TS=placebo* OR TS=(single blind*) OR TS=(double blind*)

5. #4 AND #3

Appendix 7. Criteria for risk of bias

Item	Judgement	Description
1. Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process such as: random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation.
	Unclear risk	Insufficient information about the sequence generation process to permit judgement of low or high risk.
	High risk	The investigators describe a non-random component in the sequence generation process such as: odd or even date of birth; date (or day) of admission; hospital or clinic record number; alternation; judgement of the clinician; results of a laboratory test or a series of tests; availability of the intervention.
2. Allocation concealment (selection bias)	Low risk	Investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based, and pharmacy-controlled randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.
	Unclear risk	Insufficient information to permit judgement of low or high risk. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definitive judgement.
	High risk	Investigators enrolling participants could possibly foresee assignments because one of the following methods was used: open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
3. Blinding of participants and providers (performance bias)	Low risk	Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken. Placebo should be identical to the intervention regarding appearance, colour, solubility, taste, and smell. Or no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding.
	Unclear risk	Insufficient information to permit judgement of low or high risk.

(Continued)

	High risk	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding. Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
4.Blinding of outcome assessor (detection bias)	Low risk	Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	Unclear risk	Insufficient information to permit judgement of low or high risk.
	High risk	No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding. OR Blinding of outcome assessment, but it is likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
5. Incomplete outcome data (attrition bias)	Low risk	No missing outcome data. Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias). Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups. For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate. For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size. Missing data have been imputed using appropriate methods, e.g. multiple imputation. All randomised participants are reported/analysed in the group to which they were allocated by randomisation irrespective of non-compliance and co-interventions (intention to treat).
	Unclear risk	Insufficient information to permit judgement of low or high risk (e.g. number randomised not stated, no reasons for missing data provided; number of dropouts not reported for each group).
	High risk	Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups. For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate. For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size.

(Continued)

		'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation.
6. Selective reporting (reporting bias)	Low risk	The trial protocol is available and all of the trial's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way. The trial protocol is not available, but it is clear that the published reports include all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon).
	Unclear risk	Insufficient information to permit judgement of low or high risk.
	High risk	Not all of the trial's prespecified primary outcomes have been reported. One or more primary outcomes are reported using measurements, analysis methods, or subsets of the data (e.g. subscales) that were not prespecified. One or more reported primary outcomes were not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect). One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis. The trial report fails to include results for a key outcome that would be expected to have been reported for such a trial.
7. Other bias including industry bias	Low risk	The trial appears to be free of other components that could put it at risk of bias.
	Unclear risk	The trial may or may not be free of other components that could put it at risk of bias.
	High risk	There are other factors in the trial that could put it at risk of bias, in particular the risk of industry bias will be evaluated.

CONTRIBUTIONS OF AUTHORS

All authors contributed to the review concept and design. LB and BE or LB and JR assessed studies for inclusion, risk of bias, and data extraction. LB drafted the manuscript, which was reviewed, corrected, and then accepted by all authors.

JL and CG were responsible for the planning of statistical procedures. JL performed the Trial Sequential Analyses. BG provided advice during study design, data collection and data interpretation.

DECLARATIONS OF INTEREST

LB is the sponsor-investigator of one of the studies included in this review (Baandrup 2016). A review author independent of this trial acted as the second review author, thus ensuring unbiased data extraction and 'Risk of bias' assessment.

BE has received lecture fees from Bristol-Myers Squibb, Otsuka Pharma Scandinavia AB, and Eli Lilly and Company and is part of the Advisory Board of Eli Lilly Danmark A/S, Janssen-Cilag A/S, and Takeda Pharmaceutical Company Ltd.

BG is leader of a Lundbeck Foundation Centre of Excellence for Clinical Intervention and Neuropsychiatric Schizophrenia Research, CINS. CINS is independent of H. Lundbeck A/S. The grant was awarded based on international scientific review. BG is part of the study group behind the clinical trial stated by LB in her declaration of interest.

JL, CG, and JR have no known conflicts of interest.

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- Mental health services - Capital Region of Denmark, Denmark.

  Postdoctoral grant to LB

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

JR was added as a review author because of considerable contribution to data extraction and quality assessment.

Many of the included studies were of older date, and it was therefore not possible to track and contact every first author as stated in the protocol. We contacted those authors with available and updated contact information, by email. However, many of the reported email addresses were outdated as well, and requests were returned due to unknown recipient.

Due to the poor quality of the data, we did not perform any subgroup or sensitivity analyses. However, in the single case where imputation of standard deviations was applied (Analysis 8.3) (Lader 1993), we checked that results remained substantially unchanged when excluding this trial from the analysis.

Benzodiazepine withdrawal in opioid maintenance users was mentioned as a point of focus in the protocol. However, we could only include data from two smaller studies in this review where opioid maintenance users were tapered from usual benzodiazepine use: Peles 2007 investigating melatonin and Vorma 2011 investigating valproate. Mariani 2016 also included this group of patients in a trial investigating gabapentin, but it was not possible to extract data from this trial. Due to the paucity of data, we could not draw any conclusions regarding opioid maintenance patients discontinuing benzodiazepines. However, this is an important focus for future research since there are indications that benzodiazepine use is particularly problematic in opioid maintenance users, with an increased risk of toxic overdose and death when the substances are used together (Webster 2011). Active use of benzodiazepines have been found to be present in 17% of deaths involving opioid analgesics in the US (Warner 2009). The US in particular has witnessed a rapidly increasing number of patients chronically treated with opioids (Manchikanti 2012; Skolnick 2018).

INDEX TERMS

Medical Subject Headings (MeSH)

*Withholding Treatment; Antidepressive Agents [therapeutic use]; Aspartic Acid [therapeutic use]; Benzodiazepines [administration & dosage] [*adverse effects]; Buspirone [therapeutic use]; Carbamazepine [therapeutic use]; Ethylamines [therapeutic use]; Flumazenil [therapeutic use]; Homeopathy; Imidazoles [therapeutic use]; Lithium Compounds [therapeutic use]; Melatonin [therapeutic use]; Paroxetine [therapeutic use]; Pregabalin [therapeutic use]; Progesterone [therapeutic use]; Pyridines [therapeutic use]; Randomized Controlled Trials as Topic; Substance Withdrawal Syndrome [*drug therapy]; Sulfides [therapeutic use]

MeSH check words

Adult; Humans