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[Overview of Reviews]

Efficacy and safety of pharmacological interventions for the treatment of the Alcohol Withdrawal Syndrome

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ABSTRACT

Background

Alcohol abuse and dependence represents a very serious health problem worldwide with major social, interpersonal and legal interpolations. Pharmacological treatments presently used are of uncertain effectiveness and there is even more doubt on the comparative effects and value for money.

Objectives

To summarize Cochrane reviews that assess the effectiveness and safety of pharmacological interventions in the treatment of alcohol withdrawal.

Methods

We searched the Cochrane Database of Systematic Reviews (30 November 2010). Two authors independently screened, extracted data, summarised key characteristics of the included reviews and assessed their quality using AMSTAR; the quality of the evidence was summarised according to the GRADE methodology.

Main results

Five reviews, 114 studies, 7333 participants, satisfied criteria for inclusions. The outcomes considered were alcohol withdrawal seizures, adverse events and dropouts. Comparing the five treatments with placebo, benzodiazepines performed better for seizures, three studies, 324 participants, RR 0.16 (95% CI 0.04 to 0.69), moderate quality of evidence. Comparing each of the five treatments versus specific class of drugs, benzodiazepines performed better than antipsychotics for seizures, 4 studies, 633 participants, RR 0.24 (95% CI 0.07 to 0.88) high quality of the evidence. Comparing different benzodiazepines and anticonvulsants among themselves, 28 comparisons, results never reached statistical significance but chlordiazepoxide performed better.
The quality of evidence was high for 3% of the results, moderate for 28%, low for 48% and very low for 20%.

Authors' conclusions

Among the treatments considered, benzodiazepines showed a protective benefit against seizures, when compared to placebo and a potentially protective benefit for many outcomes when compared with antipsychotics. Nevertheless, no definite conclusions about the effectiveness and safety of benzodiazepines were possible, because of the heterogeneity of the trials both in interventions and in the assessment of outcomes. Data on potential harms are sparse and fragmented. Results do not provide sufficient evidence in favour of anticonvulsants for the treatment of AWS, but anticonvulsants seem to have limited side effects. There is also not enough evidence of effectiveness and safety of baclofen, because only one study consider this treatment and of GHB for which no strong differences were observed in the comparisons with placebo, benzodiazepines and anticonvulsants.

PLAIN LANGUAGE SUMMARY

Safety and effectiveness of medications for the treatment of alcohol withdrawal syndrome

Alcohol abuse and dependence can cause serious health problems as well as interpersonal, social, interpersonal and legal consequences. Dependence on alcohol is evident by reduced control over drinking, tolerance to alcohol and withdrawal symptoms. Alcohol withdrawal syndrome develops after stopping or reducing heavy and prolonged alcohol use. The most common symptoms include sweating, a fast pulse rate, tremor, insomnia, nausea or vomiting, transient hallucinations or illusions, agitation, anxiety and seizures. These are the result of changes in the central nervous system in an attempt to maintain normal function with alcohol consumption. Different types of medications are used to safely reduce the severity of withdrawal and the abuse of alcohol.

Cochrane reviews of randomised controlled trials that examined the effectiveness and safety of medications for alcohol withdrawal syndrome were included in this overview. Participants in the review studies varied in age, gender, nationality, severity of symptoms and treatment as outpatients or inpatients. Five reviews, 114 studies, 7333 participants, were included. We considered the efficacy of the medication on alcohol withdrawal seizures, adverse events as a measure of safety and acceptability of the treatment as dropouts from the study. These outcomes were considered in 72 of the 114 studies. The treatments used were sedative benzodiazepines, anticonvulsants, baclofen, GHB and PAN. Baclofen and GHB mimic alcohol effects and can rapidly reduce symptoms. PAN (psychotropic analgesic nitrous oxide) involves administering low levels of nitrous oxide and oxygen gases so that the individual remains conscious and coherent.

Comparing the five treatments with placebo, benzodiazepines performed better for seizures (three studies, 324 participants, moderate quality of evidence). This was the only treatment with statistically significant findings. Data on potential harms were sparse and fragmented in these studies. Benzodiazepines also performed better than antipsychotics for seizures (4 studies, 633 participants, high quality of evidence).

For the majority of our results, further research is likely to have an important impact on confidence in the estimate of effect. We assessed the quality of the evidence in the included reviews using GRADE, which looks at the quality of evidence for each outcome, taking into consideration the magnitude of the effect, the relevance of the data to the clinical question being asked, the sample size in the relevant trials, the methodological quality of the trials and the consistency of the findings.

BACKGROUND

Description of the condition

Alcohol abuse and dependence represents a most serious health problem worldwide with major social, interpersonal and legal interpolations. Dependence on alcohol is associated with both physiological symptoms such as tolerance and withdrawal, and behavioural symptoms such as impaired control over drinking (Hasin 1990).

Alcohol withdrawal syndrome (AWS) is a cluster of symptoms that may occur in alcohol-dependent people. The essential feature of alcohol withdrawal is the presence of a characteristics syndrome that develops after the cessation of (or reduction in) heavy and prolonged alcohol use. (DSM-IV-R). The clinical presentation varies from mild to serious and the onset of symptoms typically may appear up to 48 hrs, and actually up to 72 hrs if we consider the uncommon case of delirium tremens after the last alcohol intake. The most common symptoms are autonomic hyperactivity (e.g. sweating or pulse rate greater than 100), tremor, insomnia, nausea or vomiting, transient visual, tactile or auditory hallucinations or illusions, psychomotor agitation, anxiety and seizures (DSM-IV-R). These symptoms involve a wide range of neurotransmitter circuits that are implicated in alcohol tolerance and reflect a homeostatic readjustment of the central nervous system (De Witte 2003; Koob 1997; Nutt 1999; Slawecki 1999). Long-term alcohol consumption affects brain receptors that undergo adaptive changes in an attempt to maintain normal function. Some of the key changes involve reduced brain gamma-aminobutyric acid (GABA) levels and GABA- receptor sensitivity (Dodd 2000; Gillman 1996; Kohl 1998; Petty 1993) and activation of glutamate systems (Tsai 1995), which lead to nervous system hyperactivity in the absence of alcohol. The advances in knowledge of neurobiology and neurochemistry have prompted the use of drugs in the treatment of alcohol dependence and withdrawal that act through these GABA pathways.

Description of the interventions

Withdrawal from alcohol may or may not require pharmacological management, depending on the amount of drinking, the presence of symptoms, the setting of detoxification (SIGN 2003) and the severity of withdrawal symptoms. However, It is important to treat AWS, in order to decrease the severity of symptoms, preventing more severe withdrawal clinical manifestations such as seizures and delirium tremens, and facilitate entry of the patient into a treatment program in order to attempt to achieve and maintain long-term abstinence from alcohol. Symptoms severity-triggered therapy using the revised Clinical Institute Withdrawal Assessment (CIWA-Ar) (Sullivan 1989) is currently recommended for the management of a patient in acute alcohol withdrawal (McKay 2004). Increasing knowledge about the involved neurotransmitter systems has prompted the development of drugs to target them. Different classes of drugs have been used to prevent and treat AWS: benzodiazepine GABAergic medications, which involve mainly the benzodiazepines, the drugs of choice in the treatment of AWS, and non-benzodiazepine GABAergic compounds, which involve carbamazepine, gabapentin, valproic acid, topiramate, Gamma-hydroxybutyric acid (GHB), baclofen, flumazenil etcetera (Leggio 2008). Benzodiazepines are established treatments for AWS (Lejoyeux 1998), but there is a growing interest in testing other medications for the treatment of AWS. Many studies have been conducted, but most of them have not included the most severe forms of AWS. Nevertheless, these studies suggest that it would be worth conducting large RCTs. Benzodiazepines have been shown to be one of the most effective classes of drugs in the management of alcohol withdrawal syndrome. Studies concerning pharmacological therapies of alcohol withdrawal has suggested that benzodiazepines are effective in reducing withdrawal severity, incidence of delirium and seizures with a greater margin of safety and lower abuse potential when compared to other therapies. Anticonvulsants drugs are also indicated for the treatment of alcohol withdrawal syndrome. The effects of GHB and alcohol on the Central nervous System (CNS) was first described in the 1970's and subsequently confirmed (Frau 1995, Colombo 1995, Colombo 1998).

How the intervention might work

Benzodiazepines have been shown to be one of the most effective class of drugs in the management of alcohol withdrawal syndrome (Holbrook 1999; Mayo-Smith 1997). The rationale of the use of benzodiazepine is to modulate central nervous system (CNS) hyperactivity, interacting with GABA receptors, due to the alcohol withdrawal.

In spite of the wide use of anticonvulsants, their exact role for the treatment of alcohol withdrawal has not yet been adequately assessed, and it is unknown whether different anticonvulsants and different regimens of administration (e.g. symptom-triggered versus fixed schedule) may have the same merits (Choi 2005; Gann 2004; Koethe 2007; Mayo-Smith 1997).

The alcohol-mimicking effects of GHB represents a rationale for using GHB in alcohol addiction treatment and in craving (Gallimberti 1989; Gallimberti 1992)

Baclofen produces its effect via modulating the GABAB receptor, similar to the drug GHB which also has the same mechanism of action and also similar effects. However, there are some pharmacological differences in that baclofen appears to have reduced abuse and dependence potential. Consistent with preclinical evidence, open-label reports demonstrated the ability of baclofen to rapidly reduce symptoms of severe AWS in alcoholic patients.

An alternative method to benzodiazepine sedation has been conceptualised and pioneered in South Africa. This treatment employs psychotropic analgesic nitrous oxide (PAN). PAN treatment involves administering low levels of nitrous oxide plus oxygen to the patient who remains conscious and coherent throughout gas administration (Gillman 1986; Gillman 1998).

In some studies, it was demonstrated that alcohol administration lead to an acute increase in magnesium excretion in the range of 167-260% greater than control subjects. Furthermore, decreased oral intake secondary to chronic alcoholism would also contribute to decreased magnesium levels (Jermain 1992). A correlation has also been found in withdrawing alcoholic patients between hypomagnesaemia and sinus tachycardia (Shane 1991).

Why it is important to do this overview

Patients, clinicians and policy makers need to know if there are any important differences between the treatment for alcohol withdrawal in terms of safety and efficacy. This overview is

aimed to summarize systematically the available evidence on the pharmacological interventions for alcohol withdrawal.

OBJECTIVES

To conduct an overview of Cochane systematic reviews that assessed the effectiveness of any pharmacological treatments, alone or in combination with others, to treat alcohol withdrawal syndrome. Any pharmacological treatment was assessed in terms of effectiveness, acceptability and safety.

METHODS

Criteria for considering reviews for inclusion

Types of studies

We included all published Cochrane systematic reviews considering pharmacological interventions aimed to treat alcohol withdrawal syndrome. Cochrane reviews employ rigorous methods
to minimise bias; and are regularly updated (Jadad 1998; Moher 2007; Shea 2007), and so represent a source of high-quality, up to-date evidence. Recent primary clinical trials not yet included in the retrieved reviews were not included.

Types of participants

We considered reviews that included alcohol dependent patients diagnosed in accordance with appropriate standardized criteria (e.g., criteria of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-R) or ICD) (DSM-IV-R) who experienced alcohol withdrawal symptoms regardless of the severity of the withdrawal manifestations. All patients were included regardless of age, gender, nationality, and outpatient or inpatient therapy.

Types of interventions

- Experimental intervention: Pharmacological interventions alone or in combination with other drugs
- Control Intervention: Placebo; Other pharmacological interventions

Types of outcomes

Efficacy outcomes

1. Alcohol withdrawal seizures
2. Alcohol withdrawal delirium
3. Alcohol withdrawal symptoms as measured by prespecified scales(as the CIWA-Ar score)
4. Craving as measured by validated scales

Safety outcomes

1. Adverse events
2. Severe, life-threatening adverse events

Acceptability outcomes

1. Dropout and dropout due to adverse events

Search methods for identification of reviews

We searched the Cochrane Database of Systematic Reviews (The Cochrane Library 30 December 2010) using the following selected mesh terms and free text relating to alcohol withdrawal:
1. Alcohol-related disorders [mesh]
2. Alcohol-Induced Disorders, Nervous System [mesh]
3. Substance Withdrawal Syndrome [mesh]
4. ((alcohol) NEAR/3 (disorder* or withdr* or abstinen* or abstain* or detox* or neuropathy or delirium))
5. #1 or #2 or #3 or #4

Data collection and analysis

Selection of reviews

Two authors independently screened the titles and abstracts of all the reviews, obtained through the search strategy. All potentially eligible reviews were obtained as full articles and two authors independently assessed them for inclusion. In doubtful or controversial cases, all identified discrepancies were discussed between the authors.

Data extraction and management

We extracted data from included reviews. The data extraction form summarise key characteristics of the review, including objectives, information on participants, interventions examined, outcomes assessed and comparisons performed. The data extraction form also summarises the results of the review for each outcome. One author extracted data and a second investigator verified the extracted data. We resolved differences by discussion and consensus.

Assessment of methodological quality of included reviews

Quality of Included Reviews

We assessed the quality of included systematic reviews using AMSTAR: A MeaSurement Tool to Assess Reviews (Shea 2007). AMSTAR assesses the degree to which review methods avoided bias by evaluating the methods against 11 distinct criteria. Each item on AMSTAR is rated as yes (clearly done), no (clearly not done), can't answer, or not applicable see Appendix 1.

One author (SM) assessed the quality of the included reviews using AMSTAR, and a second investigator (LA) verified this assessment. We resolved differences by discussion and consensus. We did not use the quality of the reviews as an inclusion criteria, but we identified and discussed differences in quality between reviews, and used the quality assessment to interpret the results.

Quality of evidence in Included reviews

- Assessment of the quality of the evidence

We assessed the quality of the evidence in included reviews according to the methodology described by the GRADE working group (Atkins 2004;Schünemann 2006). This approach involves assessing the quality of evidence for each outcome, taking into consideration the magnitude of the effect, the relevance of the data to the clinical question being asked, the sample size in the relevant trials, the methodological quality of the trials and the consistency of the findings. In the GRADE system, evidence is classified as “high”, “moderate”, “low” or “very low”. see Appendix 2

Data synthesis

Statistical presentation of results from reviews

We used a range of approaches to present the results of included reviews. Where available, we extracted and report pooled effect sizes for outcomes meta-analysed in reviews; or effect sizes from their included studies. We present results according to the statistical information available in each included review.

RESULTS

Description of included reviews

Of the 86 records identified, 76 were excluded on the basis of title, ten were considered for inclusion. Five were excluded for the following reasons: four (Fox 2003; Pani 2010; Roessner 2010a; Roessner 2010b) because type of interventions and type of outcomes considered did not satisfied the inclusion criteria and one (Smith 2009) because the outcomes did not satisfied the inclusion criteria. Five Cochrane reviews were included in this overview (Amato 2010; Gillman 2007; Leone 2010; Liu 2011; Minozzi 2010), see Figure 1 for the flow chart of included reviews and Table 1 and Table 2 for the main characteristics of included review. Regarding the Leone 2010 review, in this overview we considered only results from the six studies assessing interventions for alcohol withdrawal. All the reviews included randomised controlled trials (RCTs) examining the effectiveness, safety and overall risk-benefit of pharmacological interventions in comparison with placebo or other pharmacological treatment; in all the reviews, patients were included regardless of age, gender, nationality, and outpatient or inpatient therapy. The interventions considered were benzodiazepines, anticonvulsants, baclofen, GHB, PAN alone or in combination with other drugs compared with placebo, other pharmacological interventions and, for benzodiazepines and anticonvulsants, among themselves. The sum of studies included in the reviews is of 139, but 25 studies were included in more than one review, so the number of single included studies is 114 with a total of 7333 participants, see Table 3 for a list of the comparisons carried out.

Figure 1. Flow chart of reviews

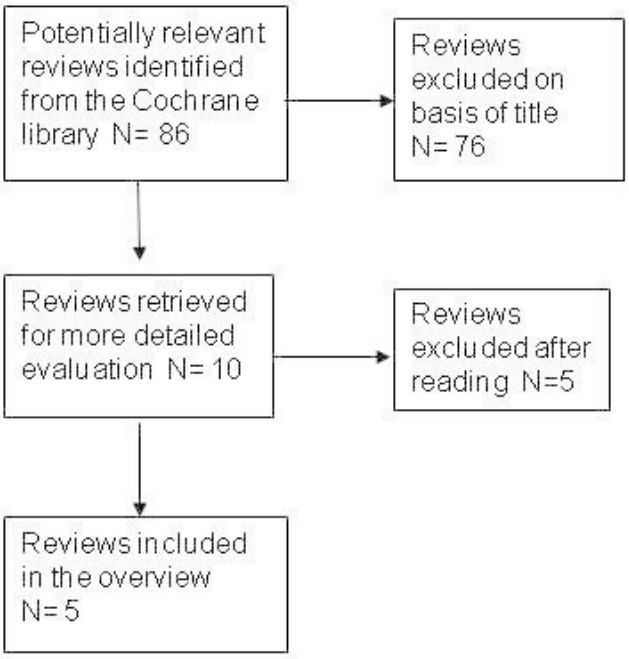

Figure 1. (Continued)

Methodological quality of included reviews

The methodological quality of the included reviews was good: all provided an a priori design; the literature search was comprehensive in all the reviews, none used the status of publication as an inclusion criteria; all provided a list of included and excluded studies, described the characteristics of included studies, assessed and documented the methodological quality of primary studies, used quality assessment results to formulate conclusions; all but one (Leone 2010) combined the results in an appropriate way (took heterogeneity into consideration); one did not perform meta-analysis because only one study was included; all stated conflict of interest. The only flaw of the included reviews related to the assessment of publication bias: three reviews (Amato 2010; Liu 2011; Minozzi 2010) planned to assess it but two (Amato 2010; Minozzi 2010) reported that funnel plot (plot of the effect estimate from each study against the sample size or effect standard error) was not used to assess the potential for bias related to the size of the trials, because all the included studies had small sample size and not statistically significant results and for one (Liu 2011) it was not possible to assess it because only one study was included ; two reviews did not appraise publication bias. See Table 4

Effect of interventions

The following results refer to primary outcomes chosen for this overview, for results related to all the outcomes considered in the five reviews, refer to the single reviews.

The outcomes considered are only primary (most relevant) outcomes and are categorized as efficacy, safety and acceptability outcomes.

- The efficacy outcome considered is: alcohol withdrawal seizures
- The safety outcome considered is: adverse events
- The acceptability outcome considered is: dropout

We present the results showing the GRADE Summary of findings tables that allow to see in a single table both results and their quality.

Comparing the five considered treatments with placebo, results were statistically significant in favour of the treatment only in one comparison: benzodiazepines performed better for seizures, results come from three studies, 324 participants, RR 0.16 (95% CI 0.04 to 0.69), and the quality of evidence was moderate. Figure 2 shows the summary of results for these comparisons.

Figure 2. Summary of findings table: treatments versus placebo

Treatments versus Placebo for alcohol withdrawal

Patient or population: patients with alcohol withdrawal
Settings: inpatient and outpatient
Intervention: Treatments versus Placebo

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk Treatments versus Placebo	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Alcohol withdrawal seizures - Benzodiazepine objective Follow-up: mean 10 days	Study population 80 per 1000 Medium risk population 69 per 1000	13 per 1000 (3 to 55) 11 per 1000 (3 to 48)	RR 0.16 (0.04 to 0.69)	324 (3 studies)	⊟⊟⊟⊟ moderate[1]	
Alcohol withdrawal seizures - Anticonvulsants objective Follow-up: mean 10 days	Study population 101 per 1000 Medium risk population 150 per 1000	53 per 1000 (25 to 108) 78 per 1000 (38 to 161)	RR 0.52 (0.25 to 1.07)	1108 (10 studies)	⊟⊟⊟⊟ moderate[2]	
Adverse events - Benzodiazepine subjective Follow-up: mean 10 days	Study population 28 per 1000 Medium risk population 46 per 1000	92 per 1000 (9 to 967) 151 per 1000 (14 to 1000)	RR 3.28 (0.31 to 34.52)	71 (2 studies)	⊟⊟⊟⊟ moderate[3]	
Adverse events - Anticonvulsant subjective Follow-up: mean 10 days	Study population 50 per 1000 Medium risk population 34 per 1000	78 per 1000 (37 to 165) 53 per 1000 (25 to 113)	RR 1.56 (0.74 to 3.31)	663 (7 studies)	⊟⊟⊟⊟ moderate[4]	
Adverse events - GHB subjective Follow-up: mean 10 days	Study population 0 per 1000 Medium risk population 0 per 1000	0 per 1000 (0 to 0) 0 per 1000 (0 to 0)	RR 16.25 (1.04 to 254.98)	23 (1 study)	⊟⊟⊟⊟ low[5]	
Dropouts - Benzodiazepine objective Follow-up: mean 10 days	Study population 164 per 1000 Medium risk population 143 per 1000	105 per 1000 (61 to 184) 92 per 1000 (53 to 160)	RR 0.64 (0.37 to 1.12)	375 (5 studies)	⊟⊟⊟⊟ moderate[6]	
Dropouts - Anticonvulsant objective Follow-up: mean 10 days	Study population 89 per 1000 Medium risk population 21 per 1000	73 per 1000 (44 to 119) 17 per 1000 (10 to 28)	RR 0.82 (0.5 to 1.34)	801 (11 studies)	⊟⊟⊟⊟ moderate[7]	
Dropouts - GHB objective Follow-up: mean 10 days	See comment	See comment	Not estimable	23 (1 study)	See comment	

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

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

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

[1] Allocation concealment unclear in all the three studies
[2] Allocation concealment unclear in the majotity of studies
[3] Small sample size, wide confidence interval

Figure 2. (Continued)

[1] Allocation concealment unclear in all the three studies
[2] Allocation concealment unclear in the majotity of studies
[3] Small sample size, wide confidence interval
[4] allocation concealment: 3/7 unclear, 1/7 no; 1/7 no blinding
[5] only one study, wide confidence interval, few participants
[6] allocation concealment unclear in 3/5 studies, blinding unclear in 1/
[7] allocation concealment: 7/11 unclear and 1/11 no; blinding no in 1 study and unclear in 1 study; sequence generation inadequate in 1 study

Comparing the five treatments versus specific class of drugs, results reached the statistical significance only in one comparison: benzodiazepines performed better than antipsychotics for seizures, 4 studies, 633 participants, 633 participants, RR 0.24 (95% CI 0.07 to 0.88) with high quality of the evidence. Figure 3 shows the summary of results for these comparisons.

Figure 3. Tratments versus specific class of drugs

Treatments versus specific class of drugs for alcohol withdrawal

Patient or population: patients with alcohol withdrawal
Settings:
Intervention: Treatments versus specific class of drugs

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk Treatments versus specific class of drugs	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Alcohol withdrawal seizures - Benzodiazepines versus anticonvulsants objective Follow-up: mean 10 days	**Study population**		**RR 2.11** (0.46 to 9.64)	479 (6 studies)	⊕⊕⊕⊖ **moderate**[1]	
	4 per 1000	**8 per 1000** (2 to 39)				
	Medium risk population					
	0 per 1000	**0 per 1000** (0 to 0)				
Alcohol withdrawal seizures - Benzodiazepines versus antipsychotics objective Follow-up: mean 10 days	**Study population**		**RR 0.24** (0.07 to 0.88)	633 (4 studies)	⊕⊕⊕⊕ **high**	
	78 per 1000	**19 per 1000** (5 to 69)				
	Medium risk population					
	56 per 1000	**13 per 1000** (4 to 49)				
Alcohol withdrawal seizures - Anticonvulsants versus antipsychotics objective Follow-up: mean 10 days	**Study population**		**RR 0.68** (0.11 to 4.34)	266 (4 studies)	⊕⊕⊕⊖ **moderate**[2]	
	38 per 1000	**26 per 1000** (4 to 165)				
	Medium risk population					
	22 per 1000	**15 per 1000** (2 to 95)				
Adverse events - Benzodiazepines versus anticonvulsants subjective Follow-up: mean 10 days	**Study population**		**RR 1.24** (0.89 to 1.73)	465 (9 studies)	⊕⊕⊖⊖ **low**[3,4]	
	160 per 1000	**198 per 1000** (142 to 277)				
	Medium risk population					
	135 per 1000	**167 per 1000** (120 to 234)				
Adverse events - Benzodiazepines versus antipsychotics subjective Follow-up: mean 10 days	**Study population**		**RR 1.28** (0.81 to 2.05)	188 (3 studies)	⊕⊕⊖⊖ **moderate**[5]	
	228 per 1000	**292 per 1000** (185 to 467)				
	Medium risk population					
	208 per 1000	**266 per 1000** (168 to 426)				
Adverse events - Anticonvulsants versus antipsychotics subjective Follow-up: mean 10 days	**Study population**		**RR 1.33** (0.46 to 3.85)	87 (2 studies)	⊕⊕⊖⊖ **low**[6,7]	
	111 per 1000	**148 per 1000** (51 to 427)				
	Medium risk population					
	124 per 1000	**165 per 1000** (57 to 477)				
Adverse events - Benzodiazepines versus GHB subjective Follow-up: mean 10 days	**Study population**		**RR 1.42** (0.5 to 4.02)	90 (2 studies)	⊕⊖⊖⊖ **very low**[8,9,10]	
	106 per 1000	**151 per 1000** (53 to 426)				
	Medium risk population					
	96 per 1000	**136 per 1000** (48 to 386)				
Dropouts - Benzodiazepines versus anticomvulsants objective Follow-up: mean 10 days	**Study population**		**RR 1.08** (0.74 to 1.58)	896 (11 studies)	⊕⊕⊕⊖ **moderate**[11]	
	103 per 1000	**111 per 1000** (76 to 163)				
	Medium risk population					
	118 per 1000	**127 per 1000** (87 to 186)				
Dropouts - Benzodiazepines verus antipsychotics objective Follow-up: mean 10 days	**Study population**		**RR 0.76** (0.36 to 1.64)	637 (4 studies)	⊕⊕⊕⊕ **high**	
	119 per 1000	**90 per 1000** (43 to 195)				
	Medium risk population					
	88 per 1000	**67 per 1000** (32 to 144)				
Dropouts - Anticonvulsants versus antipsychotics objective Follow-up: mean 10 days	**Study population**		**RR 1.06** (0.47 to 2.43)	161 (3 studies)	⊕⊕⊕⊖ **moderate**[2]	
	120 per 1000	**127 per 1000** (56 to 292)				
	Medium risk population					
	143 per 1000	**152 per 1000** (67 to 347)				
Dropouts - Benzodiazepines versus GHB objective Follow-up: mean 10 days	**Study population**		**RR 2** (0.67 to 5.94)	102 (2 studies)	⊕⊕⊖⊖ **low**[2,10]	
	78 per 1000	**156 per 1000** (52 to 463)				
	Medium risk population					
	67 per 1000	**134 per 1000** (45 to 398)				

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

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

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

[1] allcocation concealment: unclear 4/7 and inadequate 1/7

[2] all with unclear allocation concealment

[3] allocation concelament unclear in 4/9, inadequate in 1/9; blinding uncar 1/9, inadequate 3/9

[4] high heterogeneity

Figure 3. (Continued)

[2] all with unclear allocation concealment
[3] allocation concelament unclear in 4/9, inadequate in 1/9; blinding uncar 1/9, inadequate 3/9
[4] high heterogeneity
[5] allocation concealment unclear in 2/3
[6] allocation concealment unclear in 2/2
[7] imprecise and sparse data
[8] allocation concealment unclear in 2/2, blinding inadequate in 1/2, incomplete outcome data in 1/2
[9] variability of results
[10] few studies and small sample size
[11] allocation concealment unclear in 6/11, inadequate in 1/11

Comparing different benzodiazepines see Table 5 and anticonvulsants see Table 6 among themselves, results never reached statistical significance but, between benzodiazepines, chlordiazepoxide. performed better.

DISCUSSION

Summary of main results

The reviews considered many outcomes, we decided to consider in this report only the primary outcomes one related to efficacy (alcohol withdrawal seizures), one related to safety (adverse events) and one related to acceptability (dropouts). Adopting these criteria we present in this overview results from 3 outcomes, considered in 72 out the 114 studies included. Comparing the five considered treatments with placebo, results were in favour of benzodiazepines for seizures, comparing treatments versus specific class of drugs, benzodiazepines performed better than antipsychotics for seizures, although this result is not impressive considering that neuroleptics are well known pro convulsants drugs; finally comparing different benzodiazepines and anticonvulsants among themselves, results never reached statistical significance but, between benzodiazepines, chlordiazepoxide performed better.

Overall completeness and applicability of evidence

Based on these considerations, the overall results need to be interpreted with caution. For the majority of our results, those classified as moderate (28%) or low (48%) quality, further research is likely to have an important or a very important impact on confidence in the estimate of effect and may change the estimate. Furthermore, for the 20% of evidence classified as very low any estimate of effect is very uncertain. Moreover, we could not examine dose-response effects since patients were not treated with even similar doses of various treatments across RCTs. In this overview we selected only three outcomes, mainly because these were the outcomes considered by the majority of the studies and because they are all considered relevant outcomes. Weare aware that doing that we can loose useful information that in any case can be found in the original reviews. However, looking at the other outcomes in the original reviews the final judgment on the efficacy of the considered interventions is unchanged. One critical point is the choice of seizures as measure of efficacy, we are aware that it would be better to consider the overall withdrawal syndrome, unfortunately this outcome was not considered in the majority of included studies and, when considered, the way in which the data are reported varied between the studies, preventing the possibility of a cumulative analysis and this is the reason why we decided to consider seizures in this report, nevertheless these data, although not very informative, are available in the single reviews.

Quality of the evidence

The quality of evidence, rated utilising the GRADE methodology, was not so good: only two out of the 60 results (3%) are based on an high quality of evidence, both were in the comparisons between benzodiazepines and antipsychotic and only one of them reached the statistically significance, showing that benzodiazepines performed better than antipsychotics for seizures. 28% had a moderate quality of evidence, two out these 17, reached the statistically significance: one in favour of benzodiazepine versus placebo for seizures and the other one in favour of GHB versus other drugs for dropouts. 29/60 (48%) results had a low quality of evidence and 12 (20%) a very low quality. The percentages of results of low or very low quality became higher if we consider only the comparisons of different benzodiazepines and different anticonvulsants among themselves: 61% low and 32% very low.

Potential biases in the overview process

None known

Agreements and disagreements with other studies or reviews

The results of the overview are in agreement with the main results of the included reviews

AUTHORS' CONCLUSIONS

Implications for practice

With all the limits discussed above, our implications for practice are the following: Between the four treatments considered, benzodiazepines showed a protective benefit against alcohol withdrawal symptoms, in particular seizures, when compared to placebo and a potentially protective benefit for many outcomes when compared with antipsychotics drugs. Nevertheless, no definite conclusions about the effectiveness and safety of benzodiazepines were possible, because of the heterogeneity of the trials both in interventions and in the assessment of outcomes. Data on potential harms are sparse and fragmented. Results do not provide sufficient evidence in favour of anticonvulsants for the treatment of AWS, but anticonvulsants seem to have limited side effects.
There is also not enough evidence of effectiveness and safety of baclofen, because of only one study consider this treatment and of GHB for which no strong differences were observed in the comparisons with placebo, benzodiazepines and anticonvulsants.

Implications for research

Most of the available evidence are of moderate quality, suggesting the need for further research. Particularly, since benzodiazepines showed a potential benefit, further studies should test alternative drugs against them, and should investigate which benzodiazepine performed better for the treatment of alcohol withdrawal syndrome and the relative dose-response effect. To make a substantial contribution to the available evidence, new studies should enrol a large number of participants (at least 400) and consider few, important outcomes, related to the efficacy, safety and acceptability of the considered interventions, in order to allow cumulative synthesis. Adverse events for safety and dropouts for acceptability are probably the right outcomes to be considered, for efficacy the overall withdrawal syndrome should be studied. The overall withdrawal syndrome usually is an outcome assessed with scales and consistency on rating continuous outcomes in the same scales should also be achieved in order to obtain comparable information from all relevant studies.

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ADDITIONAL TABLES

Table 1. Main characteristics of included reviews

Review	Data published/assessed as update	Data Search	Population	Interventions	Comparisons Interventions	Total studies considered	N° Excluded studies	N° Included studies	N° Participants
Anticonvulsants for alcohol withdrawal	CLIB issue 3, 2010	Searches performed in December 2009;	Alcohol dependent patients who experienced alcohol withdrawal symptoms	Anticonvulsants drugs alone or combined with other drugs	Placebo; Other pharmacological interventions; Different anticonvulsants	91	35	56	4151
Benzodiazepines for alcohol withdrawal	CLIB issue 3, 2010	Searches performed in December 2009	Alcohol dependent patients who experienced alcohol withdrawal	Benzodiazepines alone or combined with other drugs	Placebo; Other pharmacological interventions; Different benzodiazepines	91	27	64	4331

Table 1. Main characteristics of included reviews *(Continued)*

			symptoms						
Gamma-hydroxybutyrate (GHB) for treatment of alcohol withdrawal and prevention of relapses	CLIB issue 2, 2010	Searches performed in September 2008;	Alcohol dependent patients in therapy with GHB to prevent or to treat AWS.	Gamma-hydroxybutyric acid (GHB) at any dosage	Placebo; Other pharmacological treatment	35	22	13	648
Baclofen for alcohol withdrawal	CLIB issue 1, 2011	Searches performed in September 2010;	Alcohol dependent patients who experienced alcohol withdrawal symptoms	Baclofen	Benzodiazepine (diazepam)	8	7	1	37
Psychotropic analgesic nitrous oxide (PAN) for alcoholic withdrawal	CLIB issue 2, 2007	Searches performed in May 2005;	Voluntary	PAN individually titrated to the clinical needs of each patient as mea-	Oxygen (placebo) and/or benzodiazepine regimen.	15	10	5	212

Table 1. Main characteristics of included reviews *(Continued)*

states	consenting subjects in alcohol withdrawal. Trials which include participants with alcoholic delirium were excluded	sured by their individual responses to the gas.	

Table 2. Country of origin of studies included in the reviews

Review	Asia	Aus-tralia/New Zealand	Europe	North America	South Africa
23 Anticonvulsants for alcohol withdrawal	1	4	33	18	0
24 Benzodiazepines for alcohol withdrawal	3	1	26	32	2
26 Gamma-hydroxybutyrate (GHB) for treatment of alcohol withdrawal and prevention of relapses	0	0	13	0	0
54. Baclofen for alcohol withdrawal	0	0	1	0	0
25 . Psychotropic analgesic nitrous oxide for alcoholic withdrawal states	0	0	0	0	5

Table 3. Comparisons carried out in the studies included in the five reviews considering treatments for alcohol withdrawal

Author	Treatment	Control
Addolorato 1999	**GHB 50mg**	**Diazepam (benzodiazepine)**
Addolorato 2005	**Diazepam (benzodiazepine)**	**Baclofen (muscle relaxant)**
Adinoff 1994	**Diazepam (benzodiazepine)**	**Placebo** **Clonidine (alpha adrenergic)** **Alprazolam (benzodiazepine**
Agricola 1982	**Carbamazepine (anticonvulsant)**	**Tiapride (antipsychotic)**
Alldredge 1989	**Phenytoin (anticonvulsant)**	**Placebo**
Ansoms 1991	**Lometazepam (benzodiazepine)**	**Zopiclone (anxyolitic)**
Anton 1997	**Diazepam (benzodiazepine)**	**Abecamil (benzodiazepine)**
Bailly 1992	**Diazepam (benzodiazepine)**	**Propranol (beta-blocking))**
Balldin 1986	**Carbamazepine (anticonvulsant) + Chlorprothixene (antipsychotic)**	**Clonidine (alpha adrenergic)**
Baumgartner 1987	**Chlordiazepoxide (benzodiazepine)**	**Clonidine (alpha adrenergic)**
Baumgartner 1991	**Chlordiazepoxide (benzodiazepine)**	**Clonidine (alpha adrenergic)**
Bjorkvist 1976	**Carbamazepine (anticonvulsant)**	**Placebo**
Blanchard 1985	**Phenobarbital (anticonvulsant)**	**Placebo**
Bonnet 2003	**Gabapentin (anticonvulsant)**	**Placebo**

Table 3. Comparisons carried out in the studies included in the five reviews considering treatments for alcohol withdrawal *(Continued)*

Borg 1986	Oxazepam (benzodiazepine)	Amobarbital (anticonvulsant) Melperone (antipsychotic)
Brown 1972	Chlordiazepoxide (benzodiazepine)	Diazepam (benzodiazepine)
Burroughs 1985	Chlordiazepoxide (benzodiazepine)	Placebo Chlormethiazole (anticonvulsant) Bromocriptine (dopamine agonist)
Ceccanti 1996	GHB 50mg	Oxazepam (benzodiazepine)
Chance 1991	Phenytoin (anticonvulsant)	Placebo
Choi 2005	Lorazepam (benzodiazepine)	Topiramate (anticonvulsant)
Croissant 2009	Chlormethiazole (anticonvulsant)	Oxcarbazepine (anticonvulsant) + Tiapride (antipsychotic)
Daeppen 2002	Oxazepam (benzodiazepine) symptom triggered	Oxazepam (benzodiazepine) fixed-schedule
Day 2004	Diazepam (benzodiazepine)	Chlordiazepoxide (benzodiazepine)
De Rooster 1983	Nitrous oxide plus oxygen	Barbiturates plus benzodiazepine
Dencker 1978	Chlormethiazole (anticonvulsant)	Piracetam (CNS stimulant)
Dion 1968	Chlordiazepoxide (benzodiazepine)	Magnesium sulphate (anticonvulsant)
Elsing 1996	GHB 50mg	Chlormethiazole (anticonvulsant)
Elsing 2009	GHB 50mg	Chlormethiazole (anticonvulsant)
Favre 2005	Diazepam (benzodiazepine)	Cyametazine (antipsychotic)
Fey 1993	Nitrous oxide	Benzodiazpine
Flygenring 1984	Carbamazepine (anticonvulsant)	Barbital (anticonvulsant)
Funderburk 1978	Chlordiazepoxide (benzodiazepine)	Ethanol
Gallimberti 1989	GHB	Placebo
Gann 2004	Chlormethiazole (anticonvulsant)	Placebo
Gillman 1986	Nitrous oxide	Diazepam (benzodiazepine)
Gillman 2004	Nitrous oxide	Diazepam (benzodiazepine)
Gillmer 1973	Oxazepam (benzodiazepine)	Benzoctamine (anxyolitic)
Glatt 1966	Chlormethiazole (anticonvulsant)	Placebo
Golbert 1967	Chlordiazepoxide (benzodiazepine)	Placebo

Table 3. Comparisons carried out in the studies included in the five reviews considering treatments for alcohol withdrawal *(Continued)*

		Promazine (anticonvulsant)
		Alcohol
		Paraldehyde (anticonvulsant) + Chloral hydrate (sedative)
Janks 1992	**Nitrous oxide**	**Benzodiazepine**
Jauhar 2000	**Chlordiazepoxide (benzodiazepine)**	**Diazepam (benzodiazepine)**
Kaim 1969	**Chlordiazepoxide (benzodiazepine)**	**Placebo**
		Chlorpromazine (antipsychotic)
		Hydroxyzine (anxyolitic)
		Thiamine (vitamine B1)
Kaim 1972	**Chlordiazepoxide (benzodiazepine)**	**Placebo**
		Paraldehyde (anticonvulsant)
		Pentobarbital (anticonvulsant)
		Perhenazine (antipsychotic)
Kalyoncu 1996	**Diazepam (benzodiazepine)**	**Carbamazepine (anticonvulsant)**
Koethe 2007	**Oxcarbazepine (anticonvulsant)**	**Placebo**
Kolin 1981	**Diazepam (benzodiazepine)**	**Alprazolam (benzodiazepine)**
Koppi 1987	**Meprobamate (anticonvulsant)**	**Caroverine (spasmolytic)**
Kramp 1978	**Diazepam (benzodiazepine)**	**Barbital (anticonvulsant)**
Krupitsky 2007	**Diazepam (benzodiazepine)**	**Placebo**
		Topiramate (anticonvulsant)
		Memantine (anticonvulsant)
		Lamotrigine (anticonvulsant)
Kumar 2009	**Lorazepam (benzodiazepine)**	**Chlordiazepoxide (benzodiazepine)**
Lambie 1980	**Valproate (anticonvulsant)**	**Placebo**
Lapierre 1983	**Chlordiazepoxide (benzodiazepine)**	**Chlormethiazole (anticonvulsant)**
Lenzenhuber 1999	**Flunitrazepam (benzodiazepine)**	**GHB**
Lepola 1984	**Chlordiazepoxide (benzodiazepine)**	**Tiapride (antipsychotic)**
Longo 2002	**Chlordiazepoxide (benzodiazepine)**	**Sodium valproate (anticonvulsant)**
		Depakote (anticonvulsant)
		Loranzepam (benzodiazepine)

Table 3. Comparisons carried out in the studies included in the five reviews considering treatments for alcohol withdrawal *(Continued)*

Lucht 2003	Diazepam (benzodiazepine)	Chlormethiazole (anticonvulsant) Carbamazepine (anticonvulsant)
Madden 1969	Chlormethiazole (anticonvulsant)	Trifluoperazine (antipsychotic)
Malcom 1989	Oxazepam (benzodiazepine)	Carbamazepine (anticonvulsant)
Malcom 2002	Lorazepam (benzodiazepine)	Carbamazepine (anticonvulsant)
Malcom 2007	Lorazepam (benzodiazepine)	Gabapentin (anticonvulsant)
Manhem 1985	Chlormethiazole (anticonvulsant)	Clonidine (adrenergic agonist)
Mariani 2006	Gabapentin (anticonvulsant)	Phenobarbital (anticonvulsant)
Martin 1975	Diazepam (benzodiazepine)	Placebo Clobazam (benzodiazepine)
MC Grath 1975	Chlordiazepoxide (benzodiazepine)	Chlormethiazole (anticonvulsant)
McLendon 1980	Chlordiazepoxide (benzodiazepine)	Placebo
Mendels 1985	Chlordiazepoxide (benzodiazepine)	Halazepam (benzodiazepine)
Mielke 1976	Diazepam (benzodiazepine)	Placebo Clorazepate (benzodiazepine)
Miller 1984	Diazepam (benzodiazepine)	Lorazepam (benzodiazepine)
Mukherjee 1983	Chlordiazepoxide (benzodiazepine)	Clobazam (benzodiazepine)
Murphy 1983	Chlormethiazole (anticonvulsant)	Placebo Tiapride (antipsychotic)
Myrick 2009	Lorazepam (benzodiazepine)	Gabapentin (anticonvulsant)
Naranjo 1983	Lorazepam (benzodiazepine)	Placebo
Nava 2007	GHB 50mg	Diazepam (benzodiazepine)
Nimmerichter 2002	GHB 50mg and 100mg	Chlormethiazole (anticonvulsant)
O'Brien 1983	Diazepam (benzodiazepine)	Lorazepam (benzodiazepine)
Overall 1973	Chlordiazepoxide (benzodiazepine)	Mesoridazine (antipsychotic)
Palestine 1976	Chlordiazepoxide (benzodiazepine)	Haloperidol (antipsychotic)
Pena-Ramos 1977	Chlordiazepoxide (benzodiazepine)	Thioridazine (antipsychotic)
Pena-Ramos 1979	Chlordiazepoxide (benzodiazepine)	Thioridazine (antipsychotic)

Table 3. Comparisons carried out in the studies included in the five reviews considering treatments for alcohol withdrawal *(Continued)*

Radouco-Thomas 1989	Chlordiazepoxide (benzodiazepine)	Phenobarbital (anticonvulsant) Tetrabamate (anticonvulsant)
Rathlev 1994	Phenytoin (anticonvulsant)	Placebo
Reoux 2001	Divalproex (anticonvulsant)	Placebo
Ritola 1981	Carbamazepine (anticonvulsant)	Chlormethiazole (anticonvulsant)
Ritson 1986	Diazepam (benzodiazepine)	Lorazepam (benzodiazepine)
Robinson 1989	Chlormethiazole (anticonvulsant)	Clonidine (adrenergic agonist)
Rosenthal 1998	Phenobarbital (anticonvulsant)	Valproate (anticonvulsant)
Rothstein 1973	Diphenylhydantoin (anticonvulsant)	Chlordiazepoxide (benzodiazepine) + Thiamine (vitamine B1)
Runion 1978	Chlordiazepoxide (benzodiazepine)	Hydroxyzine (anxyolitic)
Saitz 1994	Chlordiazepoxide (benzodiazepine) fixed-schedule	Chlordiazepoxide (benzodiazepine) symptom-triggered
Saletu 1983	Lopirazepam (benzodiazepine)	Prazepam (benzodiazepine)
Sampliner 1974	Phenytoin (anticonvulsant)	Placebo
Santo 1985	Tetrabamate (anticonvulsant)	Tiapride (antipsychotic)
Schick 2005	Carbamazepine (anticonvulsant)	Oxcarbazepine (anticonvulsant)
Seifert 2004	Carbamazepine (anticonvulsant)	Chlormethiazole (anticonvulsant)
Sellers 1977	Chlordiazepoxide (benzodiazepine)	Placebo Propranol (beta-blocking))
Sellers 1983	Diazepam (benzodiazepine)	Placebo
Solomon 1983	Chlordiazepoxide (benzodiazepine)	Lorazepam (benzodiazepine)
Spies 1996	Flunitrazepam (benzodiazepine) + Clonidine (adrenergic agonist)	Flunitrazepam (benzodiazepine) + Haloperidol (antipsychotic) Chlormethiazole (anticonvulsant) + Haloperidol (antipsychotic)
Spies 2003	Flunitrazepam (benzodiazepine) + Clonidine (adrenergic agonist) + Haloperidol (antipsychotic) infusion-titrated	Flunitrazepam (benzodiazepine) + Clonidine (adrenergic agonist) + Haloperidol (antipsychotic) bolus-titrated
Stanhope 1989	Carbamazepine (anticonvulsant)	Placebo
Stuppaeck 1992	Oxazepam (benzodiazepine)	Carbamazepine (anticonvulsant)

Table 3. Comparisons carried out in the studies included in the five reviews considering treatments for alcohol withdrawal *(Continued)*

Stuppaeck 1998	**Oxazepam (benzodiazepine)**	**Vigabatrin (anticonvulsant)**
Teijeiro 1975	**Heminiurine (anticonvulsant)**	**Phenobarbital (anticonvulsant) + Ferbamate (tranquillizes)**
Thompson 1975	**Diazepam (benzodiazepine)**	**Paraldehyde (anticonvulsant)**
Tubridy 1988	**Alprazolam (benzodiazepine)**	**Chlormethiazole (anticonvulsant)**
Wilson 1985	**Chlordiazepoxide (benzodiazepine)**	**Alprazolam (benzodiazepine)**
Worner 1994	**Diazepam (benzodiazepine)**	**Propranol (beta-blocking))**

Table 4. Quality of included reviews using AMSTAR

Amstar criteria	Amato 2010	Gillman 2007	Leone 2010	Minozzi 2010	Liu 2010
1. a priori' design	yes	yes	yes	yes	yes
2. duplicate extraction	yes	yes	yes	yes	yes
3. literature search comprehensive	yes	yes	yes	yes	yes
4 status of publication used as criteria	no	no	no	no	no
5. included and excluded list provided	yes	yes	yes	yes	yes
6. studies characteristics provided	yes	yes	yes	yes	yes
7. quality assessed and documented	yes	yes	yes	yes	yes
8. quality impacted conclusions	yes	yes	yes	yes	yes
9. methods for combining appropriate	yes	yes	no	yes	na
10. publication bias assessed	No	no	no	no	yes
11. conflicts of interest stated	yes	yes	yes	yes	yes

Table 5. Results of the comparisons between different benzodiazepines

Outcome or Subgroup	Studies	Participants	Effect Estimate R R (Random, 95% CI)
Alcohol withdrawal seizures			
Chlordiazepoxide vs Alprazolam	1	100	0.44 [0.15, 1.35]
Chlordiazepoxide vs Diazepam	1	24	0.33 [0.01, 7.45]

Table 5. Results of the comparisons between different benzodiazepines *(Continued)*

Chlordiazepoxide vs Lorazepam.	1	50	0.20 [0.01, 3.97]
Lorazepam vs. Diazepam	1	40	3.00 [0.13, 69.52]
Adverse events			
Chlordiazepoxide vs Clobazam	1	40	0.80 [0.25, 2.55]
Chlordiazepoxide vs. Diazepam	2	34	3.00 [0.14, 63.15]
Chlordiazepoxide vs. Halazepam	1	80	0.53 [0.05, 5.57]
Lorazepam vs. Diazepam	2	96	2.56 [0.35, 18.62]
Chlordiazepoxide vs Alprazolam	1	100	3.00 [0.13, 71.92]
Diazepam vs Abecamil	1	48	0.33 [0.04, 2.98]
Dropouts			
Alprazolam vs. Diazepam	2	60	0.25 [0.01, 5.03]
Chlordiazepoxide vs. Diazepam	2	41	6.00 [0.37, 96.85]
Chlordiazepoxide vs. Halazepam	1	92	2.75 [0.80, 9.51]
Chlordiazepoxide vs Clobazam	1	54	0.81 [0.32, 2.01]
Chlordiazepoxide vs Lorazepam	1	58	0.38 [0.08, 1.74]
Lorazepam vs. Diazepam	3	156	1.20 [0.54, 2.65]

Table 6. Results of the comparisons between different anticonvulsants

Outcome or Subgroup	Studies	Participants	Effect Estimate R R (Random, 95% CI)
Adverse events			
Carbamazepine versus Chlormethiazole	2	121	3.10 [1.01, 9.50]
Carbamazepine versus Barbital	1	61	1.81 [0.70, 4.68]
Chlormethiazole versus Pentobarbital	1	27	2.80 [0.12, 63.20]
Dropouts			
Carbamazepine versus Chlormethiazole	2	121	0.50 [0.16, 1.54]
Carbamazepine versus Barbital	1	60	0.07 [0.00, 1.23]
Carbamazepine versus Oxcarbazepine	1	29	3.20 [0.14, 72.62]

Table 6. Results of the comparisons between different anticonvulsants *(Continued)*

Chlormethiazole versus Pentobarbital	1	27	1.39 [0.28, 7.05]
Pentobarbital versus Paraldehyde	1	96	0.37 [0.03, 3.97]

APPENDICES

Appendix 1. AMSTAR Checklist criteria

AMSTAR criteria

1. Was an 'a priori' design provided? [Yes−the research question and inclusion criteria were established before conducting the review];
2. Was there duplicate study selection and data extraction? [Yes−at least two people working independently extracted the data and the method was reported for reaching consensus if disagreements arose];
3. Was a comprehensive literature search performed?[Yes−at least two electronic sources were searched; details of the databases, years searched and search strategy were provided; the search was supplemented by searching of reference lists of included studies, and specialised registers, and by contacting experts];
4. Was status of publication used as an exclusion criterion? [Yes−the authors stated that they excluded studies from the review based on publication status. No−authors searched for reports irrespective of publication type. They did not exclude reports based on publication from the systematic review];
5. Was a list of studies (included and excluded provided)? [Yes−a list was provided];
6. Were the characteristics of the included studies provided? [Yes−data on participants, interventions and outcomes were provided, and the range of relevant characteristics reported];
7. Was the scientific quality of the included studies assessed and reported? [Yes−predetermined methods of assessing quality were reported];
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?[Yes−the quality (and limitations) of included studies was used in the analysis, conclusions and recommendations of the review];
9. Were the methods used to combine the findings of studies appropriate?[Yes−if results were pooled statistically, heterogeneity was assessed and used to inform the decision of statistical model to be used. If heterogeneity was present, the appropriateness of combining studies was considered by review authors];
10. Was the likelihood of publication bias assessed? [Yes−publication bias was explicitly considered and assessed];
11. Was the conflict of interest stated? [Yes−sources of support were clearly acknowledged].

For all items except item 4, a rating of 'yes' is considered adequate. For item 4, a rating of 'no' (that is, the review did not exclude unpublished or grey literature) is considered adequate. A review
that adequately meets all of the 11 criteria is considered to be a review of the highest quality. For this overview we will consider reviews that achieve scores of between 8 to 11 high quality; scores
of 4 to 7 medium quality; and scores of 0 to 3 low quality. One investigator will assess the quality of the included reviews using AMSTAR, and a second investigator will verify this assessment.

Appendix 2. GRADE Criteria

Definitions are as follows:

- High – Further research is very unlikely to change confidence in the estimate of effect.
- Moderate – Further research is likely to have an important impact on confidence in the estimate of
- effect and may change the estimate.
- Low – Further research is very likely to have an important impact on confidence in the estimate of
- effect and is likely to change the estimate.
- Very low – Any estimate of effect is very uncertain

Decrease grade if:

- Serious (-1) or very serious (-2) limitation to study quality
- Important inconsistency (-1)
- Some (-1) or major (-2) uncertainty about directness

- Imprecise or sparse data (-1)
- High probability of reporting bias (-1)

Increase grade if:

- Stong evidence of association - significant relative risk of >2 (<0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1)
- Very strong evidence of association - significant relative risk of >5 (<0.2) based on direct evidence with no major threats to validity (+2)
- Evidence of a dose response gradient (+1)
- All plausible confounders would have reduced the effect (+1)

CONTRIBUTIONS OF AUTHORS

Designing the review: All authors; Screening search results: Amato, Minozzi; Screening retrieved papers against inclusion criteria,: Amato Minozzi; Extracting data from paper: Amato, Minozzi; Analysis of data: Amato, Minozzi, Davoli; Writing the review: Amato and Minozzi; Appraising quality of papers: Minozzi: Providing general advice on the review: Davoli

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- Department of Epidemiology, Lazio region, Italy.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Alcohol Withdrawal Seizures [*drug therapy]; Alcoholism [*complications]; Anticonvulsants [adverse effects] [therapeutic use]; Baclofen [therapeutic use]; Benzodiazepines [adverse effects] [therapeutic use]; Ethanol [*adverse effects]; Hydroxybutyrates [therapeutic use]; Nitrous Oxide [therapeutic use]; Substance Withdrawal Syndrome [*drug therapy]

MeSH check words

Humans