Pharmacological management of alcohol withdrawal: a meta-analysis and evidence-based practice guideline

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Authors' objectives
To provide an evidence-based practice guideline on the pharmacological management of alcohol withdrawal.

Searching
MEDLINE was searched from 1966 to June 1995 for articles published in the English language, using the MeSH terms 'substance withdrawal syndrome' and 'ethyl alcohol'. References from selected articles and reviews were also examined.

Study selection
Study designs of evaluations included in the review
Prospective controlled trials of the pharmacological management to effect any of the outcomes listed were studied if they contained methodologically-sound end points, and documented reporting of the end point in question. Only articles involving human participants and including clinical data were considered.

Specific interventions included in the review
The following interventions were studied. Benzodiazepines: slow onset drugs including chlordiazepoxide and rapid onset drugs including diazepam, lorazepam and alprazolam. Phenothiazines including promazine, paraldehyde and chlorpromazine. Other pharmacological agents studied included magnesium, beta-adrenergic antagonists, clonidine, carbamazepine, ethyl alcohol, haloperidol and thiamine. Symptom-triggered and fixed-dose regimes were studied.

Participants included in the review
No trials involving adolescents or pregnant women were studied.

Outcomes assessed in the review
The outcomes assessed were as follows: severity of alcohol withdrawal and alcohol withdrawal syndrome corresponding to the Diagnostic and Statistical Manual of Mental Disorders, withdrawal seizures, completion of withdrawal, entry into rehabilitation, adverse effects and costs.

How were decisions on the relevance of primary studies made?
The author does not state how the papers were selected for review, or how many of the reviewers performed the selection.

Assessment of study quality
The author does not report the criteria used to assess validity, or how the validity assessment was performed.

Data extraction
The data were extracted by two reviewers independently. Differences in the individual studies were analysed using the Fisher exact test and 95% confidence intervals (CIs) for the relative risk were calculated using the Taylor series.

Methods of synthesis
How were the studies combined?
Where appropriate, meta-analysis was performed by means of a random-effects model with risk differences used as a measure of effect.

How were differences between studies investigated?
The author does not state how differences between the studies were investigated.

**Results of the review**

Sixty-five prospective controlled trials involving 42 different medications were found. The findings from a number of studies are reported. Only trials where the individual results are included in this review are noted below.

Four RCTs (N=358) were used to assess the effectiveness of chlordiazepoxide versus placebo in controlling delirium.

Five RCTs (N=378) were used to assess the effectiveness of benzodiazepine versus placebo in seizure control.

Three RCTs (N=190) were used to assess the effectiveness of long-acting versus short-acting benzodiazepines in seizure control.

Two RCTs (N=389) were used to assess the effectiveness of phenothiazine versus placebo in delirium control.

Three RCTs (N=315) were used to assess the effectiveness of phenothiazine versus cross-tolerant medication, such as benzodiazepine or paraldehyde, in delirium control.

Three RCTs (N=351) were used to assess the effectiveness of phenothiazine versus cross-tolerant medication, such as benzodiazepine or paraldehyde, in seizure control.

Risk difference with benzodiazepine versus placebo for delirium: -4.9 cases of delirium per 100 patients (95% CI: -9.0, -0.7, P=0.04).

Risk difference with benzodiazepine versus placebo for seizures: -7.7 cases of seizures per 100 patients (95% CI: -12.0, -3.5, P<0.001).

Risk difference with long-acting as opposed to short-acting benzodiazepines for seizure: -6.7 cases of seizure per 100 patients (95% CI: -13.0, 0.0, P=0.07).

Risk difference with phenothiazine versus placebo for delirium: 0.0 cases of delirium per 100 patients (95% CI: -5.8, +6.6, P=0.92).

Risk difference with phenothiazine versus cross-tolerant medication for delirium: +6.6 cases of delirium per 100 patients (95% CI: 2.4, 10.8, P=0.002).

Risk difference with phenothiazine versus placebo for seizure: +4.6 cases of seizure per 100 patients (95% CI: -2.6, +11.9, P=0.19).

Risk difference with phenothiazine versus cross-tolerant medication for seizure: +11.4 cases of seizure per 100 patients (95% CI: 6.2, 16.6, P<0.001).

Beta-blockers, clonidine and carbamazepine ameliorate withdrawal severity, but evidence is inadequate to determine their effect on delirium and seizures. Individualising therapy with withdrawal scales results in the administration of significantly less medication and shorter treatment.

**Cost information**

The average wholesale costs at approximately equivalent doses are given in US dollars for seven different benzodiazepines. Changing from the continuous infusion of a short-acting agent to the use of a longer-acting agent led to decreased costs, from a mean of US$1,008.72 per patient to US$59.79 per patient.

**Authors’ conclusions**

Benzodiazepine are suitable agents for alcohol withdrawal, with the choice between different agents guided by duration.
of action, rapidity of onset and cost. Dosages should be individualised based on withdrawal severity, as measured by withdrawal scales, co-morbid illness and history of withdrawal seizures. Beta-blockers, clonidine, carbamazepine and neuroleptics may be used as adjunctive therapy but are not recommended as monotherapy.

CRD commentary
This is an ambitious review which has involved consideration of many studies. Extending the literature search beyond English language articles included in MEDLINE may have revealed more relevant studies. Details of the included studies are lacking; of particular relevance would have been the baseline characteristics of the participants, the setting, the definition of 'alcohol withdrawal', 'seizure' and 'delirium', other medications used and adverse effects. Details of validity criteria are also lacking. Many trials are briefly mentioned but no details of either the trials or the extracted data are given. There is no estimate of statistical heterogeneity between the trials used in the meta-analysis. Many of the trials for which data is given are of very small sample size, and a number of the trials have recorded no events of interest. The evidence for the recommendations is graded, but although the authors include criteria for the assignment of the grades, there are no details of the methodology used for their allocation. In view of these problems, the reported results should be treated with caution.

Bibliographic details

PubMedID
9214531

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Adrenergic beta-Antagonists /therapeutic use; Alcohol Withdrawal Delirium /drug therapy; Antipsychotic Agents /therapeutic use; Benzodiazepines /economics /therapeutic use; Carbamazepine /therapeutic use; Clinical Trials as Topic; Clonidine /therapeutic use; Ethanol /adverse effects /therapeutic use; Evidence-Based Medicine; Health Care Costs; Humans; Hypnotics and Sedatives /economics /therapeutic use; Magnesium /therapeutic use; Severity of Illness Index; Substance Withdrawal Syndrome /drug therapy; Thiamine /therapeutic use; Treatment Outcome

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.