Review: benzodiazepines are more effective than neuroleptics in reducing delirium and seizures in alcohol withdrawal


Objective
To determine, using meta-analysis, the appropriate pharmacological management of alcohol withdrawal. This information was used as the basis for a practice guideline.

Data sources
Studies were identified with Medline from 1966 to June 1995 using the terms substance withdrawal syndrome and ethyl alcohol. Bibliographies of studies and review articles were also examined.

Study selection
Studies were selected if they were controlled trials that studied humans and reported clinical end points.

Data extraction
Data were extracted in duplicate on the interventions, study quality, and patient outcomes. Patient outcomes were severity and rates of alcohol withdrawal syndrome, delirium, seizures, and completion of withdrawal; entry into rehabilitation; adverse events; and costs.

Main results
42 different medications were identified in 143 trials. 65 controlled trials were included in the meta-analysis. All 6 placebo-controlled trials of benzodiazepines showed reduced signs and symptoms of alcohol withdrawal. Benzodiazepines were better than placebo at reducing delirium (risk difference 4.9 fewer cases of delirium/100 patients, p = 0.04) and seizures (risk difference 7.7 fewer cases/100 patients, p < 0.001) (table). Long acting benzodiazepines showed a trend toward fewer seizures (p = 0.07) compared with short acting benzodiazepines. 2 studies showed that symptom triggered dosing was as effective as fixed dose treatment but patients used less medication and had shorter treatment duration. Neuroleptic agents including phenothiazines and haloperidol are less effective than benzodiazepines for reducing delirium (risk difference 6.6 more cases of delirium/100 patients, p = 0.002) and seizures (risk difference 11.4 more cases/100 patients, p = 0.001). β blockers and clonidine have been shown to reduce peripheral signs and symptoms of alcohol withdrawal but evidence is insufficient to show reductions in delirium or seizures. Magnesium has not been shown to be effective in the management of alcohol withdrawal.

Conclusion
Benzodiazepines are more effective than phenothiazines in reducing delirium and seizures in patients with alcohol withdrawal and are recommended as first line treatment for this condition.

Benzodiazepines v placebo for alcohol withdrawal*

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Benzodiazepine weighted FER</th>
<th>Placebo weighted CER</th>
<th>RRR (95% CI)</th>
<th>ARR (CI)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium</td>
<td>2.1% (8.7%)</td>
<td>83% (41 to 95)</td>
<td>6.6% (16)</td>
<td>11.4 (10 to 39)</td>
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<tr>
<td>Seizures</td>
<td>0.9% (5.7%)</td>
<td>80% (23 to 95)</td>
<td>4.8% (21)</td>
<td>11.4 (12 to 125)</td>
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</table>

*Abbreviations defined in glossary; RRR, ARR, NNT, and CI calculated from data in article.

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Commentary
Mayo-Smith et al have produced a useful meta-analysis, and the resulting guidelines are applicable in psychiatry, primary care, internal medicine, and surgery. Two medications used in Europe—chlordiazepoxide and meprobamate—were not included because the studies were not large enough to show significant reductions in seizures and delirium compared with placebo even though the drugs were shown to be effective in reducing signs and symptoms of alcohol withdrawal.

The meta-analysis also shows that when fixed dose regimens of benzodiazepines are compared with symptom triggered dosing (symptoms rated according to a nurse using a withdrawal rating scale), clinical features including seizures are well controlled and the total dosage taken by the patient tends to be less. This procedure, using for example, the Clinical Institute Withdrawal Assessment—Alcohol (revised) is recommended in the guidelines.

The meta-analysis does not review the relative benefits of inpatient compared with outpatient withdrawal from alcohol. If the withdrawal is to be assisted by medication, then the conclusions of the authors are helpful, that rapid acting benzodiazepines are more likely to be abused and therefore less applicable in outpatient treatment. It is also noteworthy that the more gradual action of the longer acting benzodiazepines may help explain why they have been shown to be more protective against seizures than shorter acting compounds.

One point of great practical importance in managing patients with alcohol withdrawal was outside the scope of this meta-analysis and guideline. Early treatment with benzodiazepines helps prevent serious complications. Too often in the general hospital delirium develops before the diagnosis is made, and management is then much more difficult. We also need guidelines on the detection of alcohol problems in the general hospital setting using interviews and blood tests.

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