

**What is the safety and efficacy of the following drug comparisons for the treatment of acute alcohol withdrawal?**

- Benzodiazepines (BZ) vs placebo
- BZ vs BZ
- BZ vs neuroleptics (NE)
- BZ vs other agents (OA) (carbamazepine or clomethiazole)
- BZ vs BZ + NE
- BZ vs BZ + OA
- NE vs Placebo
- BZ + NE vs BZ + other NE
- Carbamazepine vs placebo
- Clomethiazole vs placebo

| Ref ID: 936  |                               |   |  |                |                 |                     |   |                        |
|--|-------------------------------|---|--|----------------|-----------------|---------------------|---|------------------------|
| Reference  | Study type/<br>Evidence level | Number of patients                        | Patient characteristics  | Intervention   | Comparison      | Length of follow-up | Outcome measures  | Source of funding      |
| Ntais C, Pakos E, Kyzas P et al. Benzodiazepines for alcohol withdrawal. <i>Cochrane Database of Systematic Reviews</i> . 2005;CD005063. | Systematic Review<br><br>1++  | 21 out of 56 studies of interest (N=1068) | Adults with acute alcohol withdrawal<br><br>Studies varied with respect to patient population <ul style="list-style-type: none"> <li>• Demographics</li> <li>• Length of treatment</li> <li>• Duration of follow up</li> </ul> | Benzodiazepine | Placebo         | 8hrs – 14 days      | <ul style="list-style-type: none"> <li>• Therapeutic success (relief from acute alcohol withdrawal symptoms, and the doctor’s or patient’s global assessment of efficacy)</li> <li>• Alcohol withdrawal seizures</li> </ul> | Cochrane Collaboration |
|  |                               |   |  | Benzodiazepine | Benzodiazepine  |                     |   |                        |
|  |                               |   |  | Benzodiazepine | Anti convulsant |                     |   |                        |
|  |                               |   |  | Benzodiazepine | Neuroleptic     |                     |   |                        |
|  |                               |   |  | Benzodiazepine | Clomethiazole   |                     |   |                        |
|  |                               |   |  | Clomethiazole  | Placebo         |                     |   |                        |

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|  |  |  |  |  |  |  | <ul style="list-style-type: none"> <li>• Mortality</li> <li>• Side effects</li> <li>• Discontinuation due to side effects</li> <li>• CIWA-Ar<sup>1</sup> score (change from baseline) at 48hrs</li> <li>• CIWA-Ar score (change from baseline) at end of treatment</li> <li>• Alcohol withdrawal delirium</li> <li>• Life threatening side effects</li> </ul> |  |
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benzo (N=250) vs placebo (230) = 8 studies  
benzo (253) vs. benzo (247) = 12 studies

benzo (37) vs. neuroleptic (37) = 2 studies  
benzo (138) vs. anticonvulsant (122) = 3 studies

benzo (125) vs. clomethiazole (120) = 5 studies  
Clomethiazole (12) vs. placebo (11) = 1 study

**Effect Size**

**Note: All comparisons are for N=1 trial unless otherwise stated**

|                                    | Benzo vs. placebo   | Benzo vs. benzo  | Benzo vs. anticonvulsant  | Benzo vs. neuroleptic  | Benzo vs. Clomethiazole   |
|------------------------------------|---|--|---|--|---|
| <b>Therapeutic success</b>         | <b>Chlorodiazepoxide (N=2)</b><br><b>Lorazepam</b><br>RR: 1.40 (95%CI: 0.87-2.27) p=0.2<br>(3 of 8 studies) | <b>Lorazepam vs. diazepam</b><br>RR:0.95 (95% CI: 0.86 – 1.05) p=0.3<br><b>Chlordiazepoxide vs. diazepam</b><br>RR:1.17 ( 95% CI: 0.86 – 1.58) p=0.3<br><b>Alprazolam vs. diazepam</b><br>RR: 1 (95% CI: 0.87 – 1.13) p=0.9<br><b>Alprazolam vs. Chlordiazepoxide</b><br>RR: 0.98 (95% CI: 0.88 – 1.09) p=0.7<br>(4 of 12 studies) | -   | <b>Chlordiazepoxide vs. promazine</b><br>RR: 0.62 (95%CI: 0.37- 1.04) p=0.07<br>(1 of 2 studies) | <b>Chlordiazepoxide (n=2)</b><br>RR: 0.98 (95%CI: 0.74- 1.3) p=0.88<br>(2 of 5 studies) |
| <b>Alcohol withdrawal seizures</b> | RR: 0.16 (95% CI: 0.04-0.69) p=0.01<br>(3 of 8 studies)   | <b>Lorazepam vs. Chlordiazepoxide</b> RR:5 (95% CI: 0.25 – 99.16) p=0.3<br><b>Lorazepam vs. diazepam</b><br>RR:3 (95% CI: 0.13 – 69.52) p=0.5  | <b>Oxazepam vs. carbamazepine</b><br>RR: 3 (95%CI: 0.13- 70.74) p=0.5 | -  | <b>Alprazolam</b><br>RR: 2.87 (95%CI: 0.12- 68.68) p=0.51<br>(1 of 5 studies)           |

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|  |  | <b>Alprazolam vs. Chlordiazepoxide</b><br>RR: 2.25 (95% CI: 0.74 – 6.83) p=0.2<br>(3 of 12 studies)  | (1 of 3 studies)  |   |  |
| <b>Mortality</b>   | No deaths in 8 studies   | No deaths in 10 studies<br><b>Alprazolam vs. Chlordiazepoxide</b><br>RR: 0.33 (95% CI: 0.01 – 7.99) p=0.5<br>(1 study)   | No deaths in 3 studies  | -   | No deaths in 5 studies   |
| <b>Side effects</b>  | <b>Chlordiazepoxide</b><br>RR: 1.10 (95% CI: 0.08 – 15.36) p=0.9<br>(1 of 8 studies) | <b>Lorazepam vs. diazepam</b><br>RR:2.56 (95% CI: 0.35 – 18.62) p=0.4<br><b>Chlordiazepoxide vs. diazepam</b><br>RR:3 ( 95% CI: 0.14 – 63.15) p=0.5<br>(4 of 12 studies)   | <b>Oxazepam vs. carbamazepine</b><br>RR: 0.75 (95%CI: 0.44- 1.29) p=0.3<br>(1 of 3 studies)                 | <b>Chlordiazepoxide vs. haloperidol</b><br>RR: 1.92 (95%CI: 0.19- 19.82) p=0.58<br>(1 of 2 studies) | <b>Chlordiazepoxide (N=3)</b><br><b>Alprazolam</b><br>RR: 1.42 (95%CI: 0.68- 2.98) p=0.36<br>(4 of 5 studies)  |
| <b>Life threatening side effects</b>                             | -  | <b>Chlordiazepoxide vs. diazepam:</b> none<br><b>Alprazolam vs. Diazepam:</b> none<br><b>Alprazolam vs. Chlordiazepoxide</b><br>RR: 0.33 (95% CI: 0.01 – 7.99) p=0.5<br>(3 of 12 studies)  | -   | -   | <b>Chlordiazepoxide (N=3)</b><br><b>Alprazolam</b><br>RR: 1.45 (95%CI: 0.19- 11.24) p=0.72<br>(4 of 5 studies) |
| <b>Discontinuation due to side effects</b>                       | <b>Chlordiazepoxide</b><br>RR:0.36 (95% CI: .02 – 8.03) p=0.5<br>(2 of 8 studies)    | <b>Alprazolam vs. Chlordiazepoxide</b><br>RR: 1 (95% CI: 0.21 – 4.72) p=1<br><b>Lorazepam vs. diazepam</b><br>RR:1.66 (95% CI: 0.21 – 12.95) p=0.6<br><b>Chlordiazepoxide vs. diazepam</b><br>RR:3 ( 95% CI: 0.14 – 63.15) p=0.5<br><b>Lorazepam vs. Chlordiazepoxide:</b> none<br><b>Alprazolam vs. diazepam</b><br>RR: 0.36 (95% CI: 0.02 – 8.47) p=0.5<br>(8 of 12 studies) | <b>Oxazepam vs. carbamazepine</b><br>RR: 0.14 (95%CI: 0.01- 2.65) p=0.19<br>(1 of 3 studies)                | <b>Chlordiazepoxide vs. haloperidol</b><br>RR: 2.88 (95%CI: 0.12- 67.53) p=0.51<br>(1 of 2 studies) | <b>Chlordiazepoxide (N=3)</b><br><b>Alprazolam</b><br>RR: 0.91 (95%CI: 0.1- 8.32) p=0.94<br>(4 of 5 studies)   |
| <b>Alcohol withdrawal delirium</b>                               | -  | <b>Lorazepam vs. diazepam</b><br>RR: 5.18 (95% CI: 0.26 – 103.15) p=0.3<br><b>Alprazolam vs. Chlordiazepoxide</b><br>RR: 1 (95% CI: 0.21 – 4.72) p=1<br>(2 of 12 studies)  | <b>Oxazepam vs. carbamazepine</b><br>RR: 5 (95%CI: 0.25- 99.82) p=0.29<br>(1 of 3 studies)                  | -   | -  |
| <b>CIWA-Ar<sup>1</sup> score (change from baseline) at 48hrs</b> | -  | <b>Chlordiazepoxide vs. diazepam</b><br>RR: 4.5 (95%CI: -2.44 - 11.44) p=0.2<br>(1 of 12 studies)  | <b>Oxazepam vs. carbamazepine</b><br><b>Oxazepam vs. carbamazepine</b><br><b>Lorazepam vs carbamazepine</b> | -   | -  |

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|---|---|--|--|---|---|
|   |   |  | WMD: -0.73 (95% CI: -2.88 -1.42) p = 0.5 (3 of 3 studies)  |   |   |
| <b>CIWA-Ar score (change from baseline) at end of treatment</b> | - | <b>Chlordiazepoxide vs. diazepam</b><br>RR: 3.3 (95%CI: -4.19 - 10.79) p=0.4 (1 of 12 studies) | <b>Oxazepam vs. carbamazepine</b><br><b>Oxazepam vs. carbamazepine</b><br><b>Lorazepam vs carbamazepine</b><br>WMD: -1.04 (95% CI: -3.45 -1.38) p = 0.4 (3 of 3 studies) | - | - |

<sup>1</sup> Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar)  
WMD= Weighted mean difference

**Effect**

**BZs vs Placebo**

BZs were significantly more effective than placebo for (N=3 studies:

- Alcohol withdrawal seizures (RR: 0.16 (95% CI: 0.04-0.69) p=0.01)

There were no significant (NS) differences between BZs and placebo for:

- Therapeutic success
- Mortality
- Side effects
- Life threatening side effects
- Discontinuation due to side effects

**BZs vs BZs**

There were NS differences when one BZs was compared with another BZ for:

- Alcohol withdrawal seizures
- Therapeutic success
- Mortality
- Side effects
- Life threatening side effects
- Discontinuation due to side effects
- Alcohol withdrawal delirium
- CIWA-Ar score (change from baseline) at 48hrs

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- CIWA-Ar score (change from baseline) at end of treatment

### **BZs vs anticonvulsant**

There were NS differences when BZs were compared with anticonvulsants for:

- Alcohol withdrawal seizures
- Mortality
- Side effects
- Discontinuation due to side effects
- Alcohol withdrawal delirium
- CIWA-Ar score (change from baseline) at 48hrs
- CIWA-Ar score (change from baseline) at end of treatment

### **BZs vs neuroleptic agents (NEs)**

There were NS differences when BZs were compared with NEs for:

- Therapeutic success
- Side effects
- Discontinuation due to side effects

### **BZs vs Clomethiazole**

There were NS differences when BZs was compared with Clomethiazole for:

- Alcohol withdrawal seizures
- Therapeutic success
- Mortality
- Side effects
- Life threatening side effects
- Discontinuation due to side effects

### **Clomethiazole vs placebo**

There were no results reported for the outcomes specified