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## BENZODIAZEPINES FOR THE TREATMENT OF DELIRIUM TREMENS


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### Introduction

Delirium Tremens (DT), or alcohol withdrawal delirium, is one of three clinical stages manifested by patients experiencing alcohol withdrawal. It is considered the most severe stage and usually occurs within 3 to 5 days following the discontinuation of alcohol.[1] About 5% of patients experiencing alcohol withdrawal will progress to DT.[2]

DSM-IV diagnostic criteria for alcohol withdrawal delirium include: (1) disturbance of consciousness with reduced ability to focus, sustain, or shift attention; (2) a change in cognition or the development of a perceptual disturbance that cannot otherwise be explained; (3) disturbance develops in a short period and tends to fluctuate during the day; (4) evidence from the history, physical examination, or laboratory findings that symptoms developed during or shortly after a withdrawal syndrome.[3] Mortality rates for DT have been estimated to range from 1% - 5%. Patients most often die from cardiac arrhythmias, respiratory arrest, severe dehydration, hyperthermia, or circulatory collapse.[4] This article will review the role and use of benzodiazepines in treating alcohol withdrawal delirium.

### Guidelines for Treatment

The American Society of Addiction Medicine has prepared guidelines to ensure appropriate treatment of alcohol withdrawal. The guideline identifies three goals of treatment for detoxification of alcohol and other substances: (1) to provide a safe withdrawal from the drug(s) of dependence and enable the patient to become drug-free; (2) to provide a withdrawal that is humane and thus protects the patient's dignity; and (3) to prepare the patient for ongoing treatment of his or her dependence on alcohol or other drugs.[4]

Benzodiazepines (BZD) are the drug of choice for DT.[5] They exhibit cross-tolerance with alcohol and act directly on the gamma-amino butyric acid (GABA) system, thus, fostering a withdrawal that satisfies the tenets set forth by the American Society of Addiction Medicine. Other benefits include their anticonvulsant activity and favorable safety profile in patients with adequate cardiorespiratory reserve.

Additional drug therapy for DT includes the use of thiamine (100 mg)[2] to prevent Wernicke-Korsakoff syndrome and vitamin supplementation, including a minimum of 1 mg of folate.[1,5]

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**Table 1. Pharmacokinetics of Benzodiazepines**

| Drug | Half life | Onset of action (oral) | Active Metabolites | Route of administration |
|---|---|---|---|---|
| Diazepam (Valium) | 20-80 hours | Rapid | Yes | oral/IV |
| Lorazepam (Ativan) | 10-20 hours | Intermediate | None | oral/IV/IM |
| Midazolam (Versed) | 2-5 hours | 1– 5 minutes (IV only) | None | IV |
| Chlordiazepoxide (Librium) | 5-30 hours | Intermediate | Yes | Oral/IV |

Note: Duration of action depends on rate and extent of absorption and patient characteristics. Rapid onset = within 15 minutes, Intermediate = 15-30 minutes. Abbreviations: IV=intravenous, IM=intramuscular.

## Pharmacokinetics

Benzodiazepines are metabolized hepatically to active and/or inactive metabolites that are eliminated renally. When initiating a BZD it is important to consider the route of elimination, whether there are active metabolites, half-lives of the parent drug and any active metabolites, and the onset and duration of action.[5] Water solubility is also an important consideration when initiating treatment. Diazepam and lorazepam lie on opposite ends of the spectrum in this regard; diazepam is the most lipophilic BDZ while lorazepam has an octanol:water partition coefficient much less than diazepam. Lipophilicity alone, however, does not determine efficacy. For instance, lorazepam is the least lipophilic BZD, yet has an onset of action of 2 to 5 minutes when administered parenterally. Pharmacokinetics for different benzodiazepines are presented in **Table 1**.[1] The elimination half-lives of BZDs and their metabolites are prolonged in geriatric patients and those with liver disease. Hepatic function must be considered early in the DT treatment algorithm, since alcohol abuse is the precursor to DT. However, because there is poor correlation between the severity of hepatic disease and drug disposition, there are no formal dosing recommendations in this population.

Lorazepam has theoretical advantages over other BZDs since it does not have active metabolites.[5] Furthermore, it undergoes glucuronidation and has an intermediate half-life, which minimize the potential for accumulation in patients with hepatic disease. Due to its shorter half-life and route of metabolism, there is less concern with prolonged sedation in elderly patients. On the other hand, some have suggested that drugs with a longer half-life might be preferred due to "smoother" withdrawal. Unlike other BZDs, lorazepam possesses anti-emetic properties, which may minimize nausea associated with withdrawal. Chlordiazepoxide, a long-acting BZD, was once considered the BZD of choice for DT. However, its active metabolites can accumulate after several days of therapy, making prolonged sedation a concern.[5]

## Clinical Trials

Data regarding the use of benzodiazepines in DT appeared in the literature in the late 1950s, yet there is no consensus on which agent or dosing regimen is preferred. Clinical trials of BZDs have evaluated diverse endpoints such as mortality, duration of delirium, time required to control agitation, and adequate control of delirium. **Table 2** summarizes the results of prospective trials evaluating different agents in reducing the duration of alcohol withdrawal delirium.[13-17] A meta analysis found that benzodiazepines reduce withdrawal severity, the incidence of delirium, and seizures. Compared with neuroleptics, BZDs may improve survival.[6] β-adrenergic antagonists, clonidine, and neuroleptics were found to ameliorate withdrawal severity and can be considered useful adjuncts. Phenothiazines ameliorate withdrawal but are less effective than benzodiazepines in reducing delirium or seizures. The following conclusions can be made based on a limited number of controlled clinical trials; (1) agents with rapid onset control agitation more quickly; (2) agents with a long duration of action provide a smooth treatment course with less break-

**Table 2. Prospective Controlled Trials Reporting Duration of Delirium in Patients With Alcohol Withdrawal**

| Study | Intervention | ROA | Patients, No. | Duration, h | *P* Value |
|---|---|---|---|---|---|
| Friedhoff and Zitrin[13] | Chlorpromazine | IM/PO | 15 | 192 | < .05 |
| | Paraldehyde | | 16 | 144 | |
| Thomas and Freedman[14] | Promazine | PO | 17 | 96 | 0.04 |
| | Paraldehyde | PO | 22 | 74 | |
| Golbert et al.[15] | Promazine | PO | 5 | 134 | NS |
| | Paraldehyde/ chloral hydrate | | 11 | <24 | |
| Kaim and Klett[16] | Perphenazine | IM/PO | 46 | 77.9 | > .2 |
| | Pentobarbital | IM/PO | 41 | 80 | |
| | Paraldehyde | IM/PO | 55 | 78.4 | |
| | Chlordiazepoxide | IM/PO | 46 | 74 | |
| Thompson et al.[17] | Paraldehyde | Rectal | 17 | 57 | > .05 |
| | Diazepam | IV | 17 | 55 | |

ROA= route of administration, IM= intramuscular, PO= oral, h= hours, NS= not significant.

through symptoms; (3) when there is concern regarding prolonged sedation, such as in patients who are elderly, who have substantial liver disease or other serious concomitant medical illness, agents with shorter duration of activity may be associated with a lower risk; and (4) the cost of different benzodiazepines varies considerably.

Neuroleptic agents such as promazine and chlorpromazine are not as effective as BZDs for the treatment of DT.[6] β-adrenergic antagonists have not been adequately studied in patients with DTs.[6] A randomized, controlled clinical trial comparing transdermal clonidine with chlordiazepoxide in alcohol withdrawal concluded that clonidine was an effective treatment for alcohol withdrawal syndrome,[11] but it has not been evaluated in patients that have progressed to DT. Finally, Malcolm et al compared the effects of carbamazepine and lorazepam in ambulatory patients with alcohol withdrawal.[12] Carbamazepine was superior in preventing rebound withdrawal symptoms and reducing post-treatment drinking. However, carbamazepine has not been evaluated for the treatment of DT.

## Dosing and Administration

When using BZDs in the acute setting, the parenteral route is preferred since the onset of action is more rapid. It is important to administer the chosen BZD slowly to avoid respiratory depression, hypotension, bradycardia, or cardiac arrest.[2] The dose selected should be individualized and titrated to achieve light somnolence, which should serve as the therapeutic endpoint. Examples of medication regimens used to treat DTs include: (1) diazepam 5 mg IV (2.5 mg/min), which can be repeated a second time in 5-10 minutes, with 10 mg given as a third and fourth dose (5-10 minutes apart) up to a max of 20 mg if needed; (2) lorazepam 1 to 4 mg

**Table 3. Drug Interactions and the Effect on Benzodiazepines**

| Drug/ Drug Class | Effect on BZD |
|---|---|
| Macrolide ABX | Decreased clearance of BZD |
| Antifungals | Increased plasma concentration of BZD |
| Cimetidine | Increased plasma concentration of BZD |
| Levodopa | Decreased control of parkinsonian symptoms |
| Phenytoin | Decreased PHT concentrations |
| Carbamazepine | Decreased plasma concentration of BZD |
| Antacids | Decreased rate of GI absorption for BZD |
| Digoxin | Increased plasma half-life of digoxin |

IV every 5-15 minutes; or (3) lorazepam 1 to 40 mg IM every 30 to 60 minutes until calm, then every hour as needed to maintain light somnolence.[6] For patients requiring large doses, frequent redosing, or extended treatment, BZDs can be administered by continuous infusion, often in the intensive care unit setting. For instance, lorazepam can be started at 1 mg/hr and titrated to the desired effect.

Once the patient is stabilized, he/she can be converted to the oral form. Two commonly used dosing practices are the fixed-dose schedule and the symptom-triggered schedule.[5] In a fixed-dose model, benzodiazepines are given at specific time intervals and as needed based on the patient's withdrawal symptoms. Symptom-triggered regimens are more cost-effective because they use less total medication. The benzodiazepine is administered based on the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) score. The CIWA-Ar scale is an assessment tool, which quantifies the severity of alcohol withdrawal syndrome and also helps treat and monitor patients. Also, symptom-triggered therapy is associated with a shorter course of therapy. [4,7]

## Adverse effects

Adverse effects of BZD treatment have not been systematically collected in this population. However, these agents are generally well tolerated when an appropriate starting dose is selected and titrated cautiously. The following should be considered when evaluating the tolerability of BZD for this indication: 1) it is the adverse effect profile (i.e. somnolence) that serves as the therapeutic endpoint, 2) patients often are incoherent, 3) the toxicity of alcohol and BZDs overlap. In general, the most common adverse effects seen with BDZs are respiratory depression and sedation. Other reported effects include hypotension, confusion, dizziness, akathisia, unsteadiness, headache, depression, disorientation, amnesia, dermatitis, rash, weight gain/ loss, nausea, changes in appetite, weakness, nasal congestion, hyperventilation, and apnea. [9]

## Drug Interactions

Concomitant use of benzodiazepines with CNS-depressant drugs can enhance CNS effects such as increased sedation or respiratory depression of either agent.[8] **Table 3** lists the drug classes and their effect when used in combinations with BZDs.

## Cost

Table 4 depicts the average retail cost of the parenteral form of diazepam, lorazepam and midazolam at 3 pharmacies in Gainesville, FL. Because these patients often require large doses for an extended period of time (i.e., several days), these differences become amplified.

## Summary

Benzodiazepines are the drug class of choice for the treatment of DT. They cross-react with alcohol and act directly on the GABA system. They are beneficial in reducing agitation, preventing seizures, and providing sedation in this population. While BZDs are considered the drug of choice, there is a lack of consensus regarding which agent in the class and what dose is the most effec-

**Table 4. Retail Cost***

| Drug | Cost ($) |
|---|---|
| Lorazepam 2 mg/ml (10 ml vial) | 30.41 |
| Diazepam 5 mg/ml (10 ml vial) | 13.02 |
| Midazolam 1 mg/ml (20 ml vial) | 18.73 |

*Cost reflects average cost from 3 retail pharmacies in Gainesville, FL.

tive. Given the high rate of complications when DTs is treated inadequately, this is certainly an area worthy of further investigation.

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### Labeling Changes

- As of July 2004, the product labeling for all atypical antipsychotics on the market in the United States include a warning section cautioning prescribers regarding the association between these agents and hyperglycemia. Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma or death, has been reported in patients treated with all atypical antipsychotics.
- Topiramate (Topamax®, Ortho-McNeil) is now indicated for the prophylaxis of migraine in adults. The recommended starting dosage is 25 mg in the evening during week 1, 25 mg in the morning and in the evening during week 2, 25 mg in the morning and 50 mg in the evening during week 3, and 50 mg in the morning and in the evening during week 4; the recommended maintenance dose is 100 mg/day in two divided doses. A precaution was added concerning an association between the concomitant use of topiramate and valproic acid and hyperammonemia. The signs and symptoms of hyperammonemia abate after discontinuation of either drug.
- Fondaparinux sodium (Arixtra®, Organon Sanofi-Synthelabo): the contraindication for use in patients weighing less than 50 kg has been narrowed to those needing prophylactic therapy and undergoing hip-fracture or hip- or knee-replacement surgery.

**New Drug Approvals**

- The FDA rejected the New Drug Application submitted by AstraZeneca requesting approval of ximelagatran (Exanta®) for the prevention of strokes in patients with atrial fibrillation, prevention of venous thromboembolism in patients undergoing knee replacement therapy and long-term secondary prevention of venous thromboembolism following standard treatment. The FDA cited concerns regarding the long-term safety of Exanta®, specifically hepatic and cardiac safety.

- Insulin glulisine (Apidra®, Aventis Pharma) was approved by the FDA in April 2004. Apidra® is a rapid-acting insulin similar to insulin aspart (NovoLog®). It should be administered within 15 minutes before or 20 minutes after starting a meal.

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