To BEnzo or not to BEnzo? Is gabapentin the answer for a benzodiazepine-sparing agent for Alcohol Withdrawal Syndrome?

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Presentation Objectives

• Review the current standard of care for Alcohol Withdrawal Syndrome (AWS)

• Discuss literature on the use of gabapentin as a benzodiazepine-sparing agent

• Identify the appropriate use of gabapentin for AWS
8.2 million Alcohol Dependence

500,000 AWS Hospitalizations

33% Total ICU admissions

70% Once admitted to ICU require endotracheal intubation and mechanical ventilation

Alcohol Withdrawal Neurochemistry

GABA = γ-Aminobutyric acid

Alcohol Withdrawal Neurochemistry

Chronic Alcohol Use

Alcohol

GABA

Glutamate upregulated
Alcohol Withdrawal Neurochemistry

GABA

Glutamate upregulated

Acute Withdrawal

Minor withdrawal symptoms
• Mild anxiety
• Insomnia
• Headache
• Diaphoresis
• Palpitations
• Tremulousness
• GI upset; anorexia

Withdrawal seizures
• Single or brief flurry of generalized, tonic-clonic seizures
• Short post-ictal period
• Status epilepticus - rare

Delirium tremens
• Hallucinations
• Delirium
• Agitation
• Tachycardia
• Hypertension
• Fever
• Diaphoresis

Time from alcohol cessation (hours)
Treatment of the Acute Alcohol Withdrawal State: A Comparison of Four Drugs

• Historical trial
  • Chlordiazepoxide n=103
  • Chlorpromazine n=98
  • Hydroxyzine n=103
  • Thiamine n=103
  • Placebo n=130

• Benzodiazepines provided superior outcomes
  • Delirium tremens
  • Seizures

Results

Benzodiazepines for alcohol withdrawal

## Benzodiazepines vs. Placebo - Seizures

<table>
<thead>
<tr>
<th>Trial (year)</th>
<th>Intervention (n)</th>
<th>Seizure (n)</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaim 1972</td>
<td>CDZ = 46, PBO = 16</td>
<td>CDZ = 1, PBO = 9</td>
<td>0.14 (0.02, 1.09)</td>
</tr>
<tr>
<td>Naranjo 1983</td>
<td>LOR = 21, PBO = 20</td>
<td>LOR = 0, PBO = 1</td>
<td>0.32 (0.01, 7.38)</td>
</tr>
<tr>
<td>Sellers 1983</td>
<td>DIA = 25, PBO = 25</td>
<td>DIA = 0, PBO = 4</td>
<td>0.11 (0.01, 1.96)</td>
</tr>
<tr>
<td><strong>Total 95% CI</strong></td>
<td></td>
<td></td>
<td><strong>0.16 (0.04, 0.69)</strong></td>
</tr>
</tbody>
</table>

CDZ = chlordiazepoxide  
PBO = placebo  
LOR = lorazepam  
DIA = diazepam

### Benzodiazepines vs. Other Drug – Alcohol Withdrawal Delirium

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Golbert 1967</td>
<td>1.42 (0.70, 2.91)</td>
</tr>
<tr>
<td>Dion 1968</td>
<td>0.06 (0.00, 0.94)</td>
</tr>
<tr>
<td>Kaim 1969</td>
<td>0.20 (0.03, 1.47)</td>
</tr>
<tr>
<td>McGrath 1975</td>
<td>9.00 (0.50, 62.69)</td>
</tr>
<tr>
<td>Stuppaeck 1992</td>
<td>5.00 (0.25, 99.82)</td>
</tr>
<tr>
<td>Kalyoncu 1996</td>
<td>0.19 (0.11, 3.9)</td>
</tr>
<tr>
<td>Lucht 2003</td>
<td>0.43 (0.05, 3.73)</td>
</tr>
<tr>
<td>Favre 2005</td>
<td>0.34 (0.01, 6.15)</td>
</tr>
<tr>
<td>Total 95% CI</td>
<td>1.65 (0.21, 1.98)</td>
</tr>
</tbody>
</table>

The driving outcome for benzodiazepine use in AWS is a decrease in?

- Mild withdrawal symptoms
- Delirium tremens
- Seizure
- Alcohol use
Approach to Benzodiazepine Use for AWS

- Fixed dose
  - Scheduled regimen
- Loading dose
  - Multiple doses in a short interval
- Symptom-triggered
  - CIWA-Ar ≥ 8

The revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar) Scoring

Administer medications until CIWA score is less than 10 unless patient's level of consciousness is less than alert.

- **Lorazepam (Ativan®)** 1–4 mg PO/IV every hour PRN according to table below. Use this medication for patients with suspected or known impaired liver function, those receiving opiate medications, or those who have decreased cognition.
- **Chlordiazepoxide (Librium®)** 25–100 mg PO every hour PRN according to table below. If unable to take oral medication, give Lorazepam (Ativan®) 1–4 mg IV every 1 hour PRN according to table below.

<table>
<thead>
<tr>
<th>CIWA Score</th>
<th>Chlordiazepoxide (Librium®) Dosage</th>
<th>Lorazepam (Ativan®) Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 9</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>10 – 12</td>
<td>25 mg PO</td>
<td>1 mg PO/IV</td>
</tr>
<tr>
<td>13 – 14</td>
<td>50 mg PO</td>
<td>2 mg PO/IV</td>
</tr>
<tr>
<td>15 – 17</td>
<td>75 mg PO</td>
<td>3 mg PO/IV</td>
</tr>
<tr>
<td>18 or greater</td>
<td>100 mg PO</td>
<td>4 mg PO/IV</td>
</tr>
</tbody>
</table>

CIWA-Ar Scoring

- Total score
  - 0 - 9 : absent or minimal withdrawal
  - 10 - 19 : mild to moderate withdrawal
  - > 20 : severe withdrawal
- Maximum score 67
# Symptom-Triggered vs. Fixed Dose Benzodiazepine Treatment

<table>
<thead>
<tr>
<th>Design</th>
<th>Prospective, randomized, double-blind, controlled trial n=117</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Symptom-triggered (ST) n = 56 PBO q6h CIWA 8-15: 15mg oxazepam CIWA &gt;15: 30mg oxazepam</td>
</tr>
<tr>
<td></td>
<td>Fixed dose (FD) n = 61 Oxazepam q6h CIWA-Ar &gt; 8 additional benzodiazepines given every half hour</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Mean total benzodiazepine exposure Mean benzodiazepine utilization</td>
</tr>
</tbody>
</table>

Results

Mean Oxazepam Dose

- ST: 37.5 mg
- FD: 231.4 mg

Mean Duration of Treatment

- ST: 20 hours
- FD: 62.7 hours

Limitations of CIWA-Ar

<table>
<thead>
<tr>
<th><strong>Design</strong></th>
<th>Retrospective review of inpatients who received ST therapy according to CIWA-Ar n=124</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Random sampling of 25% of 495 patients</td>
</tr>
<tr>
<td></td>
<td>ST therapy was deemed appropriate if the medical record documented:</td>
</tr>
<tr>
<td></td>
<td>• Recent heavy alcohol consumption</td>
</tr>
<tr>
<td></td>
<td>• &gt;2 drinks per day in women and &gt;4 drinks per day in men in the week before hospital admission</td>
</tr>
<tr>
<td></td>
<td>• History of alcohol dependence or abuse</td>
</tr>
</tbody>
</table>
Results

Recent Hx of Heavy Alcohol Use
- Intact Communication: 87%
- No Intact Communication: 13%

No Recent Hx of Heavy Alcohol Use
- Intact Communication: 64%
- No Intact Communication: 36%

Concerns with Benzodiazepine Use in AWS

• Addiction potential
• Interaction with alcohol
• Psychomotor and cognitive impairment
• Drug induced delirium
• ICU transfer / need for intubation
• Rebound insomnia / anxiety
• Increased risk of return to heavy drinking

Have you seen gabapentin used in your clinical practice for AWS?

- Yes
- No
Rationale - Gabapentin for AWS

- Facilitate GABAergic mechanism
- Activity for withdrawal and dependence
- Mild adverse effect profile
- No cognitive impairment and no liver metabolism

Benzodiazepine-Sparing Management

• Withdrawal prevention and treatment
  • **Gabapentin**
    • 900mg TID x 4d
    • Then 600mg TID x 3d
    • Then 300mg TID x 2d
    • Then discontinue (9d taper)

• For severe withdrawal, prior brain injury, existing seizure disorder, or Hx of withdrawal seizure, consider adding:
  • **Divalproex (VPA)**
    • 750mg BID x 1d
    • Then 500mg BID x 5d
    • Then 250mg BID x 3d
    • Then discontinue
Benzodiazepine-Sparing Management

• Do not consider gabapentin for patients with renal insufficiency

• Continue CIWA to provide a mechanism for nursing staff to monitor patients and notify the primary service if the patient’s clinical status changes significantly

• Do not order lorazepam/chlordiazepoxide contingent upon CIWA scores; CIWA is being used to monitor the patient’s progress
Gabapentin for AWS
## Characteristics – Inpatient Prospective Studies

<table>
<thead>
<tr>
<th>Trial (year)</th>
<th>n</th>
<th>Age (years)</th>
<th>CIWA-Ar score</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonnet 2003</td>
<td>61</td>
<td>44.3 ± 7.5</td>
<td>---</td>
<td>GABA 400mg q 6h for 72h, with taper over 3d</td>
</tr>
</tbody>
</table>
| Mariani 2006 | 27 | 44.1        | 19.4 ± 0.8    | Group 1: GABA 2400mg in divided doses on day 1; tapered by 600mg daily  
Group two: Phenobarbital 240mg in divided doses on day 1; tapered by 60mg daily |
| Bonnet 2010  | 37 | 18 - 70     | ≥ 15          | GABA 800mg; early-responders received additional GABA 2400mg over the next 24 hours |

## Results – Inpatient Prospective Studies

<table>
<thead>
<tr>
<th>Trial (year)</th>
<th>Baseline CIWA-Ar score</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonnet 2003</td>
<td>---</td>
<td>Difference in rescue capsules of clomethiazole: GABA 6.2 ± 4.7 vs. PBO 6.1 ± 5.4 (mean ± SD, p = 0.96, t test)</td>
</tr>
<tr>
<td>Mariani 2006</td>
<td>19.4 ± 0.8</td>
<td>The proportion of treatment failures did not differ between treatment groups: GABA = 71% vs. Phenobarbital = 62% (p = 0.70) The proportion of patients requiring rescue (PRN) medication for breakthrough signs and symptoms of alcohol withdrawal in each treatment group: GABA = 57% vs. Phenobarbital = 38% (p=0.45)</td>
</tr>
<tr>
<td>Bonnet 2010</td>
<td>&gt; 15</td>
<td>CIWA-Ar score reduction in early responder: 800mg GABA: 17.3 ± 2.6 drop after 2h to 8.0 ± 3.6 (p&lt;0.001)</td>
</tr>
</tbody>
</table>
Summary

- Reduction in need for rescue medication
- Reduction in CIWA-Ar scores
- Reduction in alcohol cravings
- Reduction in daytime sleepiness with extended 5-7d of treatment
Limitations of Gabapentin in AWS

• Abuse and dependence
  • History of drug abuse or dependence

• Withdrawal
  • Onset 12h – 7d
  • Symptoms: delirium, sedation, confusion, and fatigue

**Gabapentin in AWS**

**Pros**
- Adjunct Tx in mild AWS
- Liver disease
- Reduction CIWA-Ar
- Reduction in daytime sleepiness
- Reduction in cravings
- Bridge from withdrawal into maintenance
- Dependence
  - Delays in return to heavy drinking
  - Reduction in drinks/week

**Cons**
- Renal dysfunction
- Abuse potential
- Under treatment leading to complications
- Lack of literature on monotherapy treatment
- Lack of literature on severe withdrawal and combination with Divalproex
True / False. There are current clinical trials underway looking at gabapentin for AWS?

- True
- False
Considerations for Future Studies

• Gabapentin dosing vs. ST benzodiazepine Tx
• Severe alcohol withdrawal
  • CIWA > 20
• Outcomes
  • Seizure
  • Delirium tremens
  • ICU admissions
Potential Role of Gabapentin use in AWS

- Safe for acute and maintenance use
- Outpatient and mild alcohol withdrawal cases
- Adjunct to benzodiazepines for moderate to severe AWS
- Advanced liver disease
Questions?

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