Pharmacologic Alternatives to Benzodiazepines for Acute Alcohol Withdrawal

- stick with or switch?

Anthony Taddei, PharmD
Clinical Pharmacy Specialist Emergency Medicine, Royal Columbian Hospital, LMPS

Michelle Hinch, BScPharm, PharmD Student, UBC

Nov 2012
Disclosure

• No conflicts to declare for both presenters
Objectives

• To review the evidence for the treatment of acute alcohol withdrawal symptoms
• To compare the efficacy and safety of the gold standard of benzodiazepines to alternatives including carbamazepine, valproic acid, phenobarbital, gabapentin/pregabalin, and topiramate
• To consider alternatives when benzodiazepines may not be optimal or practical in certain settings
Outline

• History of ETOH Withdrawal / CIWA-Ar
• Evidence for BDZ to prevent withdrawal seizures
• Evidence for Alternatives: carbamazepine, valproic acid, phenobarbital, gabapentin/pregabalin, and topiramate
• Case
• Summary of Evidence
• Recommendations
God of Wine – Bacchus / Dionysus

“Drink wine for pleasure, to end care and worry”
History of Ethanol

10000 BC: Beer jugs at Stonehenge
7000 BC: China / India: fermented rice / fruit for ceremonies
2000 BC: Persia / Greece: wine making from grapes

- used for ceremonies, rituals, medicine, daily meals
- Plato: critical of overuse and inebriation

200 Roman grape pressing and wine fermentation + storage
1000 Pre-Columbian America: Beer from maize and honey
1300 Distillation via still -> gin, whiskey, scotch
1650 Sugar cane rum: introduction to North America Natives
1700 Morphine/ETOH before surgery as sedative/analgesic
1800 Gin + Gripe Water for babies / children / mothers – F.A.S.
1920 Prohibition: Evils of ETOH; health risks
Present: Social Drinking on TV, ads

Incidence of Alcohol Withdrawal

- ~8 million alcohol dependent people in the US
- ~500,000 episodes/year of withdrawal severe enough to require hospitalization and pharmacologic treatment
  - 10% of patients will experience seizures
  - 5% experience Delirium Tremens
  - 2% mortality related to Acute Withdrawal or complications secondary to compromised general health

UpToDate: Ethanol Intoxication – accessed August 24, 2012
Alcohol’s Effect on CNS

• GABA $\rightarrow$ inhibitory neurotransmitter
• Glutamate $\rightarrow$ excitatory neurotransmitter

• Alcohol enhances effects of GABA and inhibits effects of glutamate at NMDA receptors $\rightarrow$ decreased CNS excitability
Alcohol’s Effect on CNS

- Chronic alcohol leads to up-regulation of NMDA receptors
- Abrupt cessation leads to CNS hyperexcitability
  → withdrawal signs and symptoms
  “ACUTE ALCOHOL WITHDRAWAL SYNDROME”
Acute Alcohol Withdrawal Syndrome (AWS)

- Early Phase – can start 6 hours post heavy drinking
  - Tremulousness – “the shakes”
  - Insomnia
  - Mild anxiety
  - Gastrointestinal upset; anorexia
  - Headache
  - Diaphoresis
  - Palpitations (Atrial Fibrillation – Holiday Heart)
  - Disorientation / delirium
Acute Alcohol Withdrawal Syndrome (AWS)

- Late Phase: 2 - 5 days; as late as 7 days
  - Delirium Tremens (“DTs”)
  - Seizures
  - Mortality
- Chronic ETOH Abuse: more sensitive to AWS
  - Hepatic Cirrhosis
  - Encephalopathy
  - Coagulopathy
AWS Seizures

• Tonic-Clonic Seizures usually 48 hours after cessation of habitual ETOH ingestion (over 7 drinks per day over weeks)

  – secondary to decreased GABA
  – secondary to increased Glutamate
Delirium Tremens

Patient Depiction of Delirium Tremens, 1919

Michaelsen et al. Dan Med Bul 2012;57(8):A4169

http://www.youtube.com/watch?v=291TBlwIP1c&feature=player_detailpage
Diagnosis of Alcohol Withdrawal

DSM-IV criteria

• Sudden cessation of alcohol ingestion after prolonged heavy ingestion
  AND

• at least 2 withdrawal symptoms causing significant clinical distress and impairment
Clinical Institute Withdrawal Assessment – Alcohol – revised (CIWA-Ar)

- Headache 0-7
- Orientation 0-3
- Tremor 0-7
- Sweating 0-7
- Anxiety 0-7
- Nausea (and Vomiting) 0-7
- Tactile Hallucinations 0-7
- Auditory Hallucinations 0-7
- Visual Hallucinations 0-7
- Agitation 0-7

Maximum Score = 67

Clinical Institute Withdrawal Assessment – Alcohol – revised (CIWA-Ar)

Cumulative Score

0-8   No medication necessary
9-14  Medication optional (eg seizure history)
15-20 Medication indicated for symptom control
>20   Strong risk of Delirium tremens
67   Maximum possible cumulative score

Outcome Goals – Acute Alcohol Withdrawal

Efficacy
• Prevent morbidity / Decreased Symptoms
  • seizures / delirium tremens

Safety
• Prevent adverse drug reactions related to drug therapy

Cost
• Health System costs; Length of Stay
Pharmacologic Treatment of AWS

GABA INHIBITION

NMDA EXCITATION

ETHANOL CESSATION

ETHANOL

Rx
Pharmacologic Treatment of AWS

Excitatory Synapse
NMDA Receptor

ETHANOL

Valproic acid,
Carbamazepine,
Topiramate

Pharmacologic Treatment of AWS

Inhibitory Synapse
GABA Receptor

Pharmacologic Treatment of AWS

• Benzodiazepines
  – GABA Agonists
  – Diazepam: $t_{1/2}$ 20-80 h; active metabolites
  – Lorazepam: $t_{1/2}$ 10-20 h; inactive metabolites

– Fixed Dosing (FD) vs symptom triggered (ST)
  – ST requires caregiver education for use of CIWA-Ar scoring tool
  – FD is simpler; hold if drowsy

JAMA. 1994;272:519–23
Arch Intern Med. 2002;162:1117–21
www.vhpharmsci.com/vhformulary/tools/benzodiazepines-comparison.htm
Supportive Management of AWS

• Phenothiazines, Haloperidol
  – not as effective as BDZ at reducing signs of withdrawal
  – possibly useful for hallucinations
  – can decrease seizure threshold
    • ensure adequate BDZ dosing
  – potential for QTc prolongation + Torsades
    • monitor electrolytes / replace K+, Mg++

N Engl J Med 2003;348;18
Evidence for Benzodiazepines - Cochrane

- evaluate effectiveness / safety of BDZ in treatment of AWS
- RCT 1966-2009. 64 studies, 4309 patients; all comers
- Efficacy:
  - seizures
  - delirium control
  - patient’s global assessment score
- Safety:
  - severe adverse effects

Comparisons:
  a) BDZ vs Placebo
  b) BDZ vs BDZ
  c) BDZ vs Other Rx

BDZ vs. Anticonvulsant– Outcome Delirium

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Benzodiazepine Events</th>
<th>Total Events</th>
<th>Other drugs Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Allocation concealment?</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGrath 1975</td>
<td>4</td>
<td>50</td>
<td>0</td>
<td>8.00 [0.50, 162.89]</td>
<td>Yes</td>
</tr>
<tr>
<td>Stuppaek 1992</td>
<td>2</td>
<td>29</td>
<td>0</td>
<td>5.00 [0.25, 99.82]</td>
<td>Unclear</td>
</tr>
<tr>
<td>Kalyoncu 1996</td>
<td>0</td>
<td>34</td>
<td>2</td>
<td>0.19 [0.01, 3.90]</td>
<td>Unclear</td>
</tr>
<tr>
<td>Lucht 2003</td>
<td>1</td>
<td>34</td>
<td>4</td>
<td>0.43 [0.05, 3.73]</td>
<td>No</td>
</tr>
<tr>
<td>Golbert 1967</td>
<td>6</td>
<td>12</td>
<td>1</td>
<td>6.00 [0.85, 42.59]</td>
<td>No</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>159</td>
<td>183</td>
<td>100.0%</td>
<td>1.90 [0.43, 8.38]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 13

Heterogeneity: Tau^2 = 1.18; Chi^2 = 6.88, df = 4 (P = 0.04); I^2 = 42%
Test for overall effect: Z = 0.85 (P = 0.40)
Comparison BDZ vs. Anticonvulsant – Outcome Seizure

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Benzodiazepine Events</th>
<th>Other drugs Events</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Allocation concealment?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaim 1972</td>
<td>1</td>
<td>46</td>
<td>1.20 [0.08, 18.59]</td>
<td>Yes</td>
</tr>
<tr>
<td>Radouco-Thomas 1989</td>
<td>0</td>
<td>30</td>
<td>Not estimable</td>
<td>Yes</td>
</tr>
<tr>
<td>Borg 1986</td>
<td>0</td>
<td>15</td>
<td>Not estimable</td>
<td>Unclear</td>
</tr>
<tr>
<td>Kramp 1973</td>
<td>1</td>
<td>44</td>
<td>1.97 [0.07, 16.56]</td>
<td>Unclear</td>
</tr>
<tr>
<td>Stuppaeeck 1992</td>
<td>1</td>
<td>20</td>
<td>3.00 [0.13, 70.74]</td>
<td>Unclear</td>
</tr>
<tr>
<td>Tubridy 1988</td>
<td>1</td>
<td>46</td>
<td>2.87 [0.12, 89.88]</td>
<td>Unclear</td>
</tr>
<tr>
<td>Lucht 2003</td>
<td>0</td>
<td>34</td>
<td>Not estimable</td>
<td>No</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>244</strong></td>
<td><strong>279</strong></td>
<td><strong>1.70 [0.39, 7.37]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events 4

Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 0.40$, $df = 3$ ($P = 0.94$); $I^2 = 0$

Test for overall effect: $Z = 0.71$ ($P = 0.43$)

Cochrane 2010
**Pharmacologic Treatment of AWS**

<table>
<thead>
<tr>
<th>Design</th>
<th>DB, RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>N=260; History DT secondary ETOH; ETOH 9 h prior to admission</td>
</tr>
<tr>
<td>Intervention</td>
<td>Symptom Triggered: Chlordiazepoxide 25-50mg q1h PRN for CIWA-Ar ≥ 8</td>
</tr>
<tr>
<td>Comparator</td>
<td>Fixed Dose: Chlordiazepoxide 50mg q6h x 4 doses, then 25mg q6h x 8 doses, then 25-100mg CIWA-Ar ≥ 8</td>
</tr>
<tr>
<td>Outcomes:</td>
<td><strong>Symptom Triggered</strong></td>
</tr>
<tr>
<td>Symptom triggered vs. Fixed Dose</td>
<td><strong>Total Rx mg:</strong> 100 mg (0 - 400)</td>
</tr>
<tr>
<td></td>
<td><strong>Duration of Rx:</strong> 9 h (0-43)</td>
</tr>
<tr>
<td></td>
<td>Seizures: None FD vs ST</td>
</tr>
<tr>
<td></td>
<td>JAMA. 1994;272:519–23</td>
</tr>
</tbody>
</table>
Pharmacologic Treatment of AWS

- Symptom free sooner with symptom triggered vs. fixed dose
- Less BDZ used for same CIWA-Ar score
- Less sedation with symptom triggered
- Similar study of FD vs ST using CIWA-Ar score with oxazepam
- In ST group, only 39% of patients received oxazepam

JAMA. 1994;272:519–23
Arch Intern Med 2002 ;162:1117-1121
Alcohol Withdrawal Patient Care Flow

Pt Pickup - EHS, Police, SW, Self Referral

Severe Impairment Hx

Hx
Chronic ETOH
ETOH complications
Seizure
Poly O.D.

No

Detoxification Centre or Police Holding Cell

Yes

Stable

ER Assessment
CIWA-Ar; To Psych/Addictions when cleared

Psychosocial Counseling
Nutritional Support
Addictions Med F/U - cravings

Mild Impairment with no Medical Issues

Unstable (DT, Seizure)

Rehab Half Way House Home

“Drying Out”
Example of AWS Protocol utilizing CIWA-Ar Symptom Triggered Pharmacologic Treatment

<table>
<thead>
<tr>
<th>CIWA –Ar Score</th>
<th>DIAZEPAM</th>
<th>LORAZEPAM (if pt. &gt; age 65 or has significant underlying liver disease)</th>
<th>Reassess</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 9</td>
<td>No medication</td>
<td>No medication</td>
<td>q1h x 3 then q8h x 24 hrs</td>
</tr>
<tr>
<td>10 – 19</td>
<td>10 mg po/IV q1h</td>
<td>2 mg po/SL/IV q1h</td>
<td>q1h until score &lt; 10</td>
</tr>
<tr>
<td>20 or greater</td>
<td>20 mg po/IV q1h</td>
<td>4 mg po/SL/IV q1h</td>
<td>q1h until score &lt; 10</td>
</tr>
</tbody>
</table>

Choose one of benzodiazepines listed below:

- DIAZEPAM
- LORAZEPAM

Attempt to wake patient prior to each assessment.
Case

40yo 130kg male presenting to ER 2000h via EHS;
CC: decreased LOC
HPI: found by friends after ingesting entire 26 oz Whiskey bottle; difficult to rouse; disheveled. Call to EHS
PMHx: Obstructive sleep apnea
        Chronic ETOH abuse; fatty liver
        Rx PTA: none
Allergies: NKDA
Family /Social: Smoker 1 PPD x 25 years; lives by self. Unemployed truck driver; recently fired after ETOH ingestion while driving
Case: Course in Hospital

• Initial Investigations in ER
  – Toxic: ASA, Acet, ETOH, urine tox screen
  – E7 / CBC / LFT
Case Continued – Review of Systems

HEENT: Cranial Neuro Exam Normal
CVS: BP 143/89 HR 130
  EKG: LVH
Resp: RR 22. O₂ SAT 100% RA NP
GI/GU: Nauseated, occasional wretching
Hem/Hep: ETOH 107 mmol/L (0.5 mg/dL), GTT 684 (N< 85),
       AST 851(N<35) , NH₄ 53 (N<30), ALB 28 (N>35),
       INR 1.3 (N <1.2). BG 6.8
MS/SK: Tremulous (cannot hold glass of water), diaphoretic, pruritis

Overall: Unkempt; does not want to be in ER. Willing to accept medical therapy and consider detoxification and ETOH counselling.

Initial CIWA-Ar score: 51 at 2030h
Initial Treatment in ER

EP assessment: Acute ETOH intoxication
Plan: Alcohol Withdrawal Protocol
  - Lorazepam
  - hourly CIWA-Ar score
  - Thiamine, Magnesium, Haloperidol
Consult Addictions Medicine in AM
<table>
<thead>
<tr>
<th>Time</th>
<th>CIWA-Ar</th>
<th>Lorazepam Dose</th>
<th>RR</th>
<th>O2-Sat %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2030</td>
<td>51</td>
<td>4mg IV*</td>
<td>22</td>
<td>98</td>
</tr>
<tr>
<td>2143</td>
<td>44</td>
<td>4mg IV</td>
<td>18</td>
<td>99</td>
</tr>
<tr>
<td>2240</td>
<td>41</td>
<td>4mg IV</td>
<td>18</td>
<td>97</td>
</tr>
<tr>
<td>2345</td>
<td>38</td>
<td>4mg IV</td>
<td>14</td>
<td>99</td>
</tr>
<tr>
<td>0015</td>
<td>30</td>
<td>4mg IV</td>
<td>10</td>
<td>96</td>
</tr>
<tr>
<td>0130</td>
<td>27</td>
<td>4mg IV</td>
<td>14</td>
<td>95</td>
</tr>
<tr>
<td>0235</td>
<td>22</td>
<td>4mg IV</td>
<td>12</td>
<td>98</td>
</tr>
<tr>
<td>0333</td>
<td>28</td>
<td>4mg IV + Haloperidol 5mg IV</td>
<td>14</td>
<td>99</td>
</tr>
<tr>
<td>0455</td>
<td>22</td>
<td>4mg IV</td>
<td>10</td>
<td>95</td>
</tr>
<tr>
<td>0600</td>
<td>18</td>
<td>2mg IV</td>
<td>10</td>
<td>94</td>
</tr>
<tr>
<td>0705</td>
<td>20</td>
<td>4mg IV + Haloperidol 5mg IV</td>
<td>10</td>
<td>** Pt refuses</td>
</tr>
</tbody>
</table>

Lorazepam 42mg IV + Haloperidol 10mg IV over ~11 hours

*RN notes patient combative, spitting, angry at noise and lights in ER.
Transferred to EHU (back area of ER). Refuses to wear O2 sat monitor.
RN administers lorazepam 4mg IV at 0705h, closes drapes and gives report for shift change. Patient not checked until 0745h – by Addictions physician
Case Continued

• GCS 3
• VS: no detectable pulse, no respirations
• EKG: asystole
• MS/SK: grey / blue pallor

• Patient pronounced deceased 0755h
Case Review

• Combination of Benzodiazepine + ETOH + History of obstructive apnea → respiratory anoxia and cardiac arrest

• Question by Addictions Medicine:
  – Is Alcohol Withdrawal Protocol is too aggressive for patients with co-morbidities?
  – Efficacy of Alternatives?
Other Recommendations

• Patient must be visible at all times
• Patient to wear oxygen saturation monitor at all times if BDZ administered
• Nursing Education on CIWA-Ar scoring and minimization of inter-rater variability
  – trend to score similar to previous value
  – bias re: belligerent patients
  – flumazenil dosing and availability
• Alcohol Withdrawal Protocol Modification:
  – revised to include lower intensity dosing range option
    (history Sleep Apnea, geriatrics)
Limitations of AWS Protocols utilizing CIWA-Ar and BDZ

• Inter-scorer variability
  – over and under dosing

• Some Detox Centres will not take patients on BDZ

• Caregivers not trained for CIWA-Ar?

Alternatives??
Alternatives to Benzodiazepines

- Carbamazepine
- Valproic acid
- Phenobarbital
- Gabapentin/Pregabalin
- Topiramate
Carbamazepine

Advantages
• Decreased seizure susceptibility
• Enhances GABA activity
• No abuse potential
• No respiratory depression
• Does not potentiate alcohol intoxication

Disadvantages:
• Hepatic elimination
# Carbamazepine
Malcolm et al, 1989

<table>
<thead>
<tr>
<th>Design</th>
<th>SC, DB, RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>n=86; CIWA-Ar ≥ 20; alcohol dependent</td>
</tr>
<tr>
<td>Intervention</td>
<td>Carbamazepine 200mg PO QID</td>
</tr>
<tr>
<td>Comparator</td>
<td>Oxazepam 30mg PO QID</td>
</tr>
<tr>
<td>Outcomes</td>
<td><strong>CIWA-Ar score over 7 day tx</strong>: NSS at any time point</td>
</tr>
<tr>
<td></td>
<td>Seizures: Not reported</td>
</tr>
<tr>
<td></td>
<td>Delirium Tremens: Not reported</td>
</tr>
</tbody>
</table>

Carbamazepine vs. Oxazepam

Change in CIWA-Ar score over 7 days: NSS

### Carbamazepine
Stuppaecck et al, 1992

<table>
<thead>
<tr>
<th>Design</th>
<th>SC, DB, RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>n=60; CIWA-Ar ≥ 20; inpatients; alcohol dependence</td>
</tr>
<tr>
<td>Intervention</td>
<td>CMZ PO 800mg/day x 3 days, then 600mg/day x 4 days</td>
</tr>
<tr>
<td>Comparator</td>
<td>Oxazepam PO 120mg/day x 3 days, then 90mg/day x 4 days</td>
</tr>
<tr>
<td>Outcomes (CMZ vs. Oxazepam)</td>
<td><strong>CIWA-Ar score over 7 day tx:</strong> NSS days 1-5; SS on days 6 and 7</td>
</tr>
<tr>
<td></td>
<td>Patients with Seizures: 0 vs. 1</td>
</tr>
<tr>
<td></td>
<td>Patients with Delirium Tremens: 0 vs. 2</td>
</tr>
</tbody>
</table>

Carbamazepine vs. Oxazepam

### Carbamazepine
**Malcolm et al, 2002**

<table>
<thead>
<tr>
<th>Design</th>
<th>SC, DB, RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>n=136; outpatients; Mean CIWA-Ar score =13</td>
</tr>
<tr>
<td>Intervention</td>
<td>CMZ 600-800mg/d x 1 day, then tapered until 200mg/day on day 5</td>
</tr>
<tr>
<td>Comparator</td>
<td>Lorazepam 6-8mg/d x 1 day, then tapered until 2mg/day on day 5</td>
</tr>
<tr>
<td>Outcomes (CMZ vs. Lorazepam)</td>
<td><strong>CIWA-Ar score at day 7</strong>: 4.5 vs. 7.5 (p=0.01)</td>
</tr>
<tr>
<td></td>
<td>Seizures: None in either group</td>
</tr>
<tr>
<td></td>
<td>Delirium Tremens: None in either group</td>
</tr>
</tbody>
</table>

Carbamazepine vs. Lorazepam

Day 5 Treatment stopped

## Summary of Effectiveness

<table>
<thead>
<tr>
<th>Alternatives to Benzodiazepines</th>
<th>Better Efficacy?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>✗</td>
</tr>
<tr>
<td>Valproic Acid</td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td></td>
</tr>
<tr>
<td>Gabapentin/Pregabalin</td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td></td>
</tr>
</tbody>
</table>
Valproic Acid

Advantages
• Decreased seizure susceptibility
• Enhances GABA activity
• No abuse potential
• No respiratory depression
• Insignificant interaction with alcohol

Disadvantages:
• Hepatic elimination
Valproic Acid

- 2 small, randomized studies showed no clinical benefit over lorazepam for reduction of CIWA-Ar score
- No seizures or delirium tremens in either study
- Mild ADRs reported with both treatments

Longo et al. J of Addictive Diseases 2002;21(2):55-64
## Summary of Effectiveness

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<thead>
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</tr>
<tr>
<td>Phenobarbital</td>
<td></td>
</tr>
<tr>
<td>Gabapentin/Pregabalin</td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td></td>
</tr>
</tbody>
</table>
Phenobarbital

**Advantages:**
- Low abuse potential
- Long duration of action ($t1/2 = 50-300$ hours)
- Multiple routes of administration
- Decreased seizure susceptibility

**Disadvantages:**
- Respiratory depression
- Narrow therapeutic window (Additive toxicity with ETOH – post discharge concern)
### Phenobarbital

Michaelsen et al, 2010

<table>
<thead>
<tr>
<th>Study</th>
<th>Retrospective analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Population</td>
<td>n=194; admitted to psychiatric department for DT treatment</td>
</tr>
<tr>
<td>Intervention</td>
<td>Phenobarbital 100-200mg PO/IV q1h prn</td>
</tr>
<tr>
<td>Comparator</td>
<td>Diazepam 10-20mg IV q1h prn</td>
</tr>
<tr>
<td>Outcomes: PB vs. Diazepam</td>
<td><strong>DT duration (days):</strong> 5.85 ± 6.3 vs. 6.64 ± 4.2 (NSS)</td>
</tr>
<tr>
<td></td>
<td>Seizures: 26% vs. 17% (NSS)</td>
</tr>
<tr>
<td></td>
<td>Mortality (patients): 3 vs. 1 (NSS)</td>
</tr>
</tbody>
</table>

Michaelsen et al. Dan Med Bul 2010;57(8):A4169
# Phenobarbital

**Hendey et al, 2011**

<table>
<thead>
<tr>
<th>Study</th>
<th>SC, DB, RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>n=44; Baseline CIWA-Ar Score: PB = 15; Loraz = 16.8</td>
</tr>
<tr>
<td>Intervention</td>
<td>Phenobarbital 230mg IV LD + 130mg IV PRN</td>
</tr>
<tr>
<td>Comparator</td>
<td>Lorazepam 2mg IV PRN</td>
</tr>
<tr>
<td>Outcomes: Phenobarbital vs. BZD</td>
<td><strong>CIWA score at time ER Discharge:</strong> 5.4 vs. 4.2 (NSS)</td>
</tr>
<tr>
<td></td>
<td>Seizures: 1 vs. 0 (NSS)</td>
</tr>
<tr>
<td></td>
<td>Delirium Tremens: Not reported</td>
</tr>
</tbody>
</table>

Phenobarbital vs. BZD

CIWA-Ar Score at Baseline and time of ER discharge

## Summary of Effectiveness

<table>
<thead>
<tr>
<th>Alternatives to Benzodiazepines</th>
<th>Better Efficacy?</th>
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<tbody>
<tr>
<td>Carbamazepine</td>
<td>✗</td>
</tr>
<tr>
<td>Valproic Acid</td>
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</tr>
<tr>
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<td></td>
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<tr>
<td>Topiramate</td>
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</table>
Gabapentin/Pregabalin

**Advantages:**
- Renal excretion
- Reduced alcohol consumption in animal studies
- Decreased seizure susceptibility

**Disadvantages:**
- Case reports of abuse
- Withdrawal symptoms (confusion, agitation, diaphoresis, hallucinations)
# Gabapentin

**Myrick et al, 2009**

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<tr>
<th>Study</th>
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<tr>
<td>Patient</td>
<td>n=100; outpatient; mean CIWA-Ar = 12; blood alcohol level ≤ 0.10%</td>
</tr>
<tr>
<td>Intervention</td>
<td>Gabapentin – 600mg/900mg/1200mg daily divided TID and tapered over 4 days</td>
</tr>
<tr>
<td>Comparator</td>
<td>Lorazepam 2mg TID x 3 days, then 2mg BID x 1 day</td>
</tr>
<tr>
<td>Results</td>
<td>CIWA score on Day 7 (3 days after end of treatment):</td>
</tr>
<tr>
<td></td>
<td>900mg = 3 vs. Loraz = 4 (NSS)</td>
</tr>
<tr>
<td></td>
<td>1200mg = 2 vs. Loraz = 4 (p=0.009)</td>
</tr>
<tr>
<td></td>
<td>600mg: D/C tx arm due to seizures in 2 pts</td>
</tr>
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<td>Delirium Tremens: none reported in any group</td>
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Gabapentin vs. Lorazepam

Change in CIWA-AR score over time in days

Day 4, Treatment Stopped

### Pregabalin

**Martinotti et al, 2009**

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<tr>
<th>Study</th>
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<tbody>
<tr>
<td><strong>Patient Population</strong></td>
<td>n=74; CIWA-AR &gt; 10; &gt;80g alcohol in past 24 hours; alcohol dependence</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Pregabalin (max 450mg/day) PRN according to CIWA-Ar score</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>Lorazepam (max 10mg/day) PRN</td>
</tr>
<tr>
<td><strong>Outcomes:</strong></td>
<td><strong>CIWA score over 15 days of treatment:</strong> NSS at any time point</td>
</tr>
<tr>
<td></td>
<td>Seizures/DT: none reported</td>
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Pregabalin vs. Lorazepam

# Summary of Effectiveness

## Alternatives to Benzodiazepines

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Topiramate

• Decreased seizure susceptibility
• Enhances GABA activity and kainate receptor antagonism
• No abuse potential
• No respiratory depression
• Suppression of dopamine release and possible inhibition of reinforcing effects of alcohol
**Topiramate**  
Krupitsky et al., 2007

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<tr>
<td>Patient Population</td>
<td>N=76; male inpatients; EtOH consumption 8-48 hrs prior to admission; CIWA-Ar ≥ 10</td>
</tr>
<tr>
<td>Intervention</td>
<td>Topiramate 25mg PO QID x 7 days</td>
</tr>
</tbody>
</table>
| Comparator | Diazepam 10mg PO TID x 7 days  
Or Placebo |
| Results | **Mean difference in CIWA-Ar from placebo average over test days:**  
Topiramate = -1.21 (95% CI -2.76, 0.34)  
Diazepam = -1.64 (95% CI -3.2, -0.08)  
Seizures/DT: not reported |

Summary of Effectiveness

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Anticonvulsant Summary

• Anticonvulsants show similar reduction in CIWA-Ar scores without an increase in seizures, delirium tremens, or adverse effects

• But:
  – Not all studies compared versus standard symptom triggered BZD dosing
  – Not assessing severe alcohol withdrawal
  – Dosing not established for all anticonvulsants
Possible Place in Therapy of Alternatives

• Ongoing trials to assess benefit and risk of anticonvulsants for long term alcohol management

• May be useful for discharge to half-way houses or detoxification centers
  – Fixed Dose regimen easier for caregiver
  – some outpatient sites do not allow pt to be on BDZ and/or cannot do CIWA-Ar scoring
Take Home Message

• Alternative pharmacologic agents not superior
  – Few comparative RCTs
• BDZ remains evidence-based gold standard

• Continue use of CIWA-Ar scoring and current ETOH Withdrawal Protocol with BDZ
  – With high risk patients (eg obstructive sleep apnea), consider lower doses
• Accurate scoring correlates with appropriate dosing when using validated protocols
  – Ensure staff education: CIWA-Ar scoring, use of AWS protocol
  – Monitor for drug effect and adverse effects frequently

In this evidence-based world: “If it ain’t broke, don’t fix it”
  – Farmer, Georgia, USA ~ 1930s

www.Phrases.org.uk
Direct to Consumer (DTC) Marketing for Alcohol - Pharmaceutical Style

http://www.youtube.com/watch?v=vgChjrgwhH8
Questions?

Torresponda, Positano, Amalfi, Italy
Valproic Acid
Myrick et al

<table>
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<tr>
<th>Design</th>
<th>Myrick (2000), OL, R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>n=11; CIWA-Ar score ≥ 6</td>
</tr>
<tr>
<td>Intervention</td>
<td>Valproic Acid 500mg q8h + Lorazepam 2mg PRN</td>
</tr>
<tr>
<td>Comparator</td>
<td>Lorazepam 2mg q8h PRN</td>
</tr>
</tbody>
</table>
| Outcomes     | Group by CIWA-Ar score (q8h):
                       VA decline > Loraz, p≤0.01
                       Seizures: none reported
                       Delirium Tremens: none reported |

Valproic Acid vs. Lorazepam

CIWA score measured at 8 hour intervals over 5 days

Valproic Acid
Longo et al

<table>
<thead>
<tr>
<th>Design</th>
<th>Longo (2002), OL, R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>n=16; Mean CIWA-Ar = 12)</td>
</tr>
<tr>
<td>Intervention</td>
<td>Valproic Acid 20mg/kg/day PO div BID</td>
</tr>
<tr>
<td>Comparator</td>
<td>Lorazepam or chordiazepoxide PRN</td>
</tr>
<tr>
<td>Outcomes: Valproic acid vs BZD</td>
<td>CIWA-Ar score at 12h and 24h: 12h: 6 vs 9 24h: 3 vs 5 (P value not reported)</td>
</tr>
<tr>
<td></td>
<td>Seizures: None reported</td>
</tr>
<tr>
<td></td>
<td>Delirium Tremens: None reported</td>
</tr>
</tbody>
</table>

Longo et al. J of Addictive Diseases 2002;21(2):55-64
Valproic Acid vs. BZD

Change in CIWA-AR Score

Longo et al. J of Addictive Diseases 2002;21(2):55-64