ANTICONVULSANTS IN ALCOHOL WITHDRAWAL TREATMENT: A BETTER WAY?

RICHARD RIES MD
PROFESSOR OF PSYCHIATRY AND DIRECTOR
ADDICITONS DIVISION, UW / HARBORVIEW
RRIES@UW.EDU

HUGH MYRICK MD
MUSC  CHARLESTON SC
SIGNS AND SYMPTOMS OF EARLY ALCOHOL WITHDRAWAL

Autonomic Hyperactivity (increased P, BP)
Tremor
Diaphoresis
Nausea / Vomiting
Anxiety-Agitation
Insomnia
Transient Perceptual Disturbances
Seizures
MILD-TO-MODERATE ALCOHOL WITHDRAWAL

• Time course
  - 6 to 8 hours after last drink
  - Peaks at 24 to 48 hours after last drink

• Symptoms may include some or all of the following:
  - Anxiety, insomnia, irritability, tremor, headache, gastrointestinal disturbance, diaphoresis, increased blood pressure and heart rate

SEVERE ALCOHOL WITHDRAWAL

• Alcohol withdrawal seizures
  • Usually occur 6 to 48 hours from last drink

• Delirium tremens
  • Gradual onset 2 to 3 days from last drink, peak at 4 to 5 days

MEDICATION TREATMENT OF UNCOMPLICATED WITHDRAWAL

• Gold Standard: Benzodiazepines
  – Long acting vs. Short Acting
  – Symptom-triggered vs. Scheduled

• Barbiturates, Paraldehyde, Alcohol

• Antacid, Thiamine, MVI, Magnesium

• Anticonvulsants ?

• Baclofen ?

• We are NOT talking about DT/ICU mangement
# BENZODIAZEPINES

<table>
<thead>
<tr>
<th>Compound</th>
<th>Onset</th>
<th>Distribution</th>
<th>Half-life</th>
<th>Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>Int</td>
<td>Int</td>
<td>Int</td>
<td>Renal</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>Slow</td>
<td>Int</td>
<td>Short</td>
<td>Renal</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Fast</td>
<td>Fast</td>
<td>Long</td>
<td>Liver</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>Int</td>
<td>Slow</td>
<td>Long</td>
<td>Liver</td>
</tr>
</tbody>
</table>

Onset for PO administration; all are fast IV.
Lorazepam most reliable if IM administration needed.
SYMPTOM-TRIGGERED

SAITZ ET AL JAMA AUG 17, 1994; 272(7): 519

• 50mg Q6h x 4 then 25mg Q6h x 8 plus 25-100mg prn
  – 68 hrs medication administration
  – 425mg / patient

• Scheduled Placebo plus prn
  – 9 hrs medication administration
  – 100 mg / patient

• Same Rates of Improvement and complications

• Faster DC from Inpt Detox
UNCOMPLICATED WITHDRAWAL INPATIENT PROTOCOL  *EXAMPLE*

- Chlordiazepoxide
- Give 50 mg PRN CIWA-Ar 10 or Greater
  - continue hourly until CIWA-Ar score < 10
  - hold if signs of alcohol or benzodiazepine intoxication
- Measure CIWA-Ar 1 Hour After Each Dose
  - and at least Q shift until acute withdrawal resolved
- *Modify if Needed* for Individual Patients
- Diazepam 10mg, Lorazepam 2mg
TRADITIONAL ALCOHOL WITHDRAWAL TREATMENT

• Substitute cross-dependent drug (BZ)
• Gradually withdraw substitute drug
• Supplement vitamins and minerals
  ✷ thiamine
  ✷ folic acid
  ✷ multi-vitamin
• Supportive treatment
  ✷ decrease stimulation
• Increasingly an outpatient procedure
RELATIVE INDICATIONS FOR OUTPATIENT ALCOHOL DETOXIFICATION

- Negative history for DT’s and Seizures
- Medically stable/Negative lab work up
- Psychiatrically stable
- Stable living environment / Social Support
- Ability to follow up in clinic
- Mild-moderate withdrawal
- Good adherence—esp with BZP’s
- Low risk for BZP diversion/abuse
- Anti-convulsants may be superior
ANTICONVULSANTS FOR ALCOHOL WITHDRAWAL

• Anti-kindling
• GABA Enhancement
• Glutamate Inhibition
• Used More Extensively in Europe
• Recent RCT’s in USA may outperform BZP’s
• May hold special advantages for Out-pt Detox.
## ANTICONVULSANTS AS ALCOHOL DETOXIFICATION AGENTS

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>– No abuse liability</td>
<td>Limited clinical experience</td>
</tr>
<tr>
<td>– Seizure medication</td>
<td>Heme side effects</td>
</tr>
<tr>
<td>– Neuroprotective</td>
<td>Liver toxicity (not gabap)</td>
</tr>
<tr>
<td>– Cognition</td>
<td>Confusion (topiramate)</td>
</tr>
<tr>
<td>– Extended time Rx</td>
<td>? DT role/Acute Sz role ?</td>
</tr>
</tbody>
</table>
EFFECTS OF ALCOHOL ON NEUROCHEMICAL BALANCE

Normal Acute Alcohol Intake Chronic Intake/Dependence

GABA Glutamate GABA Glutamate GABA Glutamate

Acute Withdrawal

GABA Glutamate


Ries- 2012
ANTICONVULSANTS- “POST ACUTE WITHDRAWAL”

• Alcohol withdrawal physiological symptoms may be abnormal for weeks or months in many individuals
  1. Dexamethasone suppression tests
  2. Abnormal sleep and Sleep EEG’s

• Anticonvulsants may be used for weeks or months for ongoing alcohol withdrawal Rx without causing tolerance and dependence

• How to identify which pts need this? (likely repeat WD’s and extended detox sx in past (not researched)
EEG sleep studies in "pure" primary alcoholism during subacute withdrawal: relationships to normal controls, age, and other clinical variables.

Gillin JC¹, Smith TL, Irwin M, Kripke DF, Schuckit M.

EEG sleep recordings in 34 controls and 31 inpatients with relatively pure primary alcoholism who had been abstinent for about 17 days.

Compared with normal controls, primary alcoholics
1. took longer to fall asleep,
2. slept less, and had poor sleep efficiency.
3. Sleep loss reflected reduced non-rapid eye movement (NREM) sleep, especially stage 2 sleep, stage 4 sleep, and total delta (stage 3 and 4) sleep.
4. Alcoholic patients had higher REM density of the first REM period.
5. The number of drinks per drinking day in the 3 months before admission was directly related to the duration of the first REM period.
6. In addition, the maximum number of withdrawal symptoms the patient had ever experienced was inversely related to the amount of delta sleep
Altered Sleep Physiology in Chronic Alcoholics: reversal with abstinence

Williams HL  Rundell OH Jr

Abstract
Somnograms obtained from recently abstinent chronic alcoholics reveal gross disruption succinctly described as "fractured" sleep. Sleep onset is delayed and the rhythmic properties of the sleep pattern are markedly disturbed with numerous brief arousals and changes of sleep stage.

Excessive stage 1 and stage rapid eye movement sleep are present while the high voltage slow wave sleep is markedly reduced or absent.

With continued sobriety (9 mo or more) the sleep stage percentages tend to return to normal levels, but the disruption of the sleep pattern persists after as much as 21 mo of abstinence.
The Differential Effects of Medication on Mood, Sleep Disturbance, and Work Ability in Outpatient Alcohol Detoxification.


A double-blind, randomized controlled trial of patients (n = 136) meeting DSM-IV criteria for alcohol withdrawal and stratified based on detoxification history were treated with carbamazepine or lorazepam for 5 days on a fixed dose tapering schedule. Mood symptoms improved for all subjects regardless of medication or detoxification history.

**Carbamazepine > Lorazepam for:**

Reducing **anxiety**  (p = 0.0007)

Improving **sleep**  (p = 0.0186)
Clinical Institute Withdrawal Assessment (adjusted for time since last drink)

- Carbamazepine
- Lorazepam

Study Day

Baseline 2 3 4 5 6 7 8 9 10 11 12

End of Medication

*p=0.007
CARBAMAZEPINE VS. LORAZEPAM IN ALCOHOL WITHDRAWAL

• Double-blind, outpatient trial (n=136)

• CIWA-AR ≥ 10 for inclusion

• 5 day tapering dose
  – CBZ = 600-800 mg/d tapered to 200mg by day 5
  – LZ = 6-8 mg/d tapered to 2 mg by day 5

• Compared single (0-1) vs. multiple (≥ 2) medicated detoxifications
**DRINKS PER DRINKING DAY: DAY 6 TO DAY 12**

- **CBZ/0-1**: n=30
- **LZP/0-1**: n=40
- **CBZ/≥2**: n=8
- **LZP/≥2**: n=11

* main effect, $P=.0032$; Drug x Detox Hx, $P=.0333$. 

ZUNG ANXIETY SCALE SCORES

Zung Anxiety Scale Score

Assessment Day

Day 1
Day 5
Day 12

CBZ
LZP

*CBZ < LZP, P = .0007.
IMPROVEMENT IN SLEEP

Assessment Day

Score

CBZ

Malcom 2002
CARBAMAZEPINE

• Carbamazepine
  – 600-800mg/d tapered over 5 days
  – vs. lorazepam 6-8mg/d tapered over 5 days
• Equal Reduction in CIWA-Ar Scores
• Better Sleep, Greater Reduction in Anxiety
• Less Rebound, Reduced Alcohol Use
Valproic Acid for Alcohol Withdrawal

<table>
<thead>
<tr>
<th>Investigators (Year)</th>
<th>$N$</th>
<th>Design</th>
<th>Comparison</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bocci and Beretta (1976)</td>
<td>25</td>
<td>Open-label</td>
<td>None</td>
<td>“56%” improved CGI</td>
</tr>
<tr>
<td>Brausseur (1978)</td>
<td>375</td>
<td>Open-label</td>
<td>None</td>
<td>“78%” excellent results</td>
</tr>
<tr>
<td>Lambie, Johnson, Vijayasenan, and Whiteside (1980)</td>
<td>49</td>
<td>Open-label</td>
<td>VPA vs. no treatment</td>
<td>VPA=0 seizures</td>
</tr>
<tr>
<td>Hillbom et al. (1989)</td>
<td>138</td>
<td>Double-blind</td>
<td>PBO, VPA, CBZ</td>
<td>No treatment=5 seizures</td>
</tr>
<tr>
<td>Hammer and Brady (1996)</td>
<td>2</td>
<td>Case reports</td>
<td>None</td>
<td>Rapid CIWA ↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BPAD/AW</td>
<td></td>
<td>Reduced LZP pm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Reduced mania</td>
</tr>
<tr>
<td>Rosenthal, Perkel, Singh, Anand, and Miner (1998)</td>
<td>37</td>
<td>Randomized open-label</td>
<td>Phenobarbital</td>
<td>Half as much pm phenobarbital in VPA group</td>
</tr>
<tr>
<td>Myrick, Brady, and Malcolm (2000)</td>
<td>11</td>
<td>Open-label</td>
<td>LZP</td>
<td>VPA=LZP</td>
</tr>
<tr>
<td>Reoux et al. (2001)</td>
<td>36</td>
<td>Double-blind</td>
<td>Oxazepam</td>
<td>Use of VPA led to reduced use of oxazepam</td>
</tr>
</tbody>
</table>
BMC Psychiatry.

Treatment of alcohol dependence with Low-Dose Topiramate: an open-label controlled study.

Paparrigopoulos T  Tzavellas E  Karaiskos D  Kourlaba G  Liappas I

Following a 7-10 day inpatient alcohol detoxification protocol, 90 patients were assigned to receive either topiramate (up to 75 mg per day) in addition to psychotherapeutic treatment (n = 30) or psychotherapy alone (n = 60).

Relapse rate  Topiramate (66.7%)  vs (85.5%), (p = 0.043).

Time to relapse longer  (log rank test, p = 0.008).

median duration of abstinence Top 10 wks vs 4 weeks

No serious side effects of topiramate were recorded throughout the study.
GABAPENTIN VS. LORAZEPAM IN ALCOHOL WITHDRAWAL

• Double-blind, outpatient trial (n=101)

• CIWA-AR ≥ 10 for inclusion

• Tapering dose
  – GBP = 900-1200 mg/d tapered over 4 days
  – LZ = 6 mg/d tapered over 4 days

• Acoustic Startle assessed on Days 0, 4, and 7

• Follow-up at Day 7 and 12

Myrick et al, ACER, 2009
DRINKING ODDS

Comparisons NS

- Myrick 2009

Odds(Drink)

Treatment

Follow-up-Day 12

low dose gabapentin
Hi Dose Gabapentin
Lorazepam

≤ .05
≤ .07
Gabapentin treatment for alcohol dependence: a randomized clinical trial

Mason BJ

DESIGN, PARTICIPANTS AND SETTING:
A 12-week, double-blind, placebo-controlled, randomized dose-ranging trial of 150 men and women with current alcohol dependence
Oral gabapentin (dosages of 0 [placebo], 900 mg, or 1800 mg/d) and concomitant manual-guided counseling.

RESULTS

Abstinence Rate
4.1% placebo group,
11.1% 900-mg group, and
17.0 % 1800-mg group (P = .04 for linear dose effect; number needed to treat [NNT] = 8 for 1800 mg).

No Heavy Drinking rate
22.5% placebo
29.6 % 900-mg group
44.7 % 1800-mg group (P = .02 for linear dose effect; NNT = 5 for 1800 mg)

Gabapentin treatment for alcohol dependence: a randomized clinical trial
Mason BJ

Placebo vs Gabapentin 900 mg or 1800 mg/day
Similar linear dose effects were obtained with measures of

mood (P = .001)
sleep (P < .001)
craving (P = .03)

There were no serious drug-related adverse events, and terminations owing to adverse events (9 of 150 participants), time in the study (mean [SD], 9.1 [3.8] weeks), and rate of study completion (85 of 150 participants) did not differ among groups.
A total of 150 alcohol-dependent individuals were randomly assigned to a 16-week course of naltrexone alone (50 mg/day [N=50]), naltrexone (50 mg/day) with gabapentin (up to 1,200 mg/day [N=50]) added for the first 6 weeks, or double placebo (N=50). All participants received medical management.

RESULTS:
During the first 6 weeks, the naltrexone-gabapentin group had a longer interval to heavy drinking than the naltrexone-alone group, which had an interval similar to that of the placebo group; poor sleep was associated with more drinking in the naltrexone-alone group but not in the naltrexone-gabapentin group, while a history of alcohol withdrawal was associated with better response in the naltrexone-gabapentin group.
DETOX IS NOT ADDICTION TREATMENT

• Acute Stabilization
  – Safe Physiological/Psychological Withdrawal
  – Environment Conducive to Abstinence

• Assessment
  – Co-occurring Disorders, Treatment Needs

• Preparation for Addiction Treatment
  – Begin Forming Therapeutic Relationships
  – Psychosocial Stabilization
  – Begin to Address Co-occurring Disorders
  – Relapse Prevention Strategies

• Initiate Pharmacotherapy ??
no heavy drinking rate
22.5% (95% CI, 13.6%-37.2%)
29.6% (95% CI, 19.1%-42.8%) 900-mg group,
44.7% (95% CI, 31.4%-58.8%) 1800-mg group (P = .02  NNT = 5).

Similar linear dose related effects for:
mood  (F2 = 7.37; P = .001),
sleep  (F2 = 136; P < .001),
craving

No group differences in serious side effects of completion rate (85 of 150 participants)
RELATIVE INDICATIONS FOR OUTPATIENT ALCOHOL DETOXIFICATION

• Negative history for DT’s and Seizures
• Medically stable/Negative lab work up
• Psychiatrically stable
• Stable living environment / Social Support
• Ability to follow up in clinic
• Mild-moderate withdrawal
• Good adherence—esp with BZP’s
• Low risk for BZP diversion/abuse
• Anti-convulsants may be superior
ANTICONVULSANTS FOR SLEEP IN RECOVERING ALCOHOLICS AND ADDICTS

• Sedative
• Non-Addictive
• Relatively friendly to REM architecture
• Direct Rx of Post Acute WD for Alc and BZP’s
• Certain Pain syndromes (neurogenic pain- Gabapentin/ Cluster headaches Topiramate
• ? Enhance Sobriety/Decrease drinking
Principles of Addiction Medicine
Edition V

Senior Editor:
Richard K. Ries, MD, FAPA, FASAM

Associate Editors: David A. Fiellin, MD; Shannon C. Miller, MD, FASAM, FAPA, CMRO; Richard Saitz, MD, MPH, FACP, FASAM

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QUESTIONS ?

CASES AND CONUNDRUMS