STOPPING THE SHAKES:
Advanced Concepts in Alcohol Withdrawal Management

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DISCLOSURES
• No financial, litigational, or other conflicts of interest to disclose

OBJECTIVES
• Briefly discuss receptor changes with chronic alcohol consumption
• Review various approaches for therapy with GABA agonists
• Discuss novel drugs/approaches
NEUROTRANSMITTER/RECEPTOR

• Excitatory NTs work on receptors to open calcium channels leading to excitatory postsynaptic potentials
  – Primary excitatory: glutamate (NMDA)

• Inhibitory NT work on chloride channels to hyperpolarize cells
  – Primary inhibitory: GABA

CHRONIC ETOH: RECEPTOR CHANGES

• Chronic EtOH produces several effects:
  – NMDA
    1) Increase number
    2) Increase affinity and sensitivity for glutamate
    3) Increase synaptic [glutamate]
  – GABA:
    1) Decrease number
    2) Decrease function
    3) Decrease synaptic [GABA]

GABA_A RECEPTOR

• Heteromeric protein complex consisting of multiple subunits
  – α (1-6), β (1-3), γ (1-3), δ, ε, θ, π

• Various sub-units responsible for different effects of EtOH

• Chronic EtOH
  – ↓ α 1, α 2, and α 3
  – ↓ α 4, β 1, β 2, β 3, γ 1, and γ 2
**GABA<sub>A</sub> RECEPTOR**

- Chronic EtOH causes decreased expression of α1 and increased expression of α4
- Substitution of α4 for α1 receptor results in decreased efficacy and potency of various benzodiazepines.

**NEUROTRANSMITTER CHANGES WITH CHRONIC ETHANOL**

<table>
<thead>
<tr>
<th>↓ FUNCTION</th>
<th>↑ FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>GABA</td>
<td>Glutamate</td>
</tr>
<tr>
<td>DA</td>
<td>NE</td>
</tr>
<tr>
<td>SHT</td>
<td>ACh</td>
</tr>
<tr>
<td>Adenosine</td>
<td>Corticotropin-Releasing Factor (CRF)</td>
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</tbody>
</table>

**AWS TREATMENT BACKGROUND**

- Late 1950’s to early 1960s, AWS recognized to occur as a result of cessation of EtOH, not poor diet
- Various treatments proposed
  - Reserpine
  - Phenothiazines
  - Meprobamate
  - BZD
  - Paraldehyde
Case 39-2012: A 55-Year-Old Man with Alcoholism, Recurrent Seizures, and Agitation

- Restraints for agitation
- Benzodiazepines
- Metoprolol for tachycardia
- Haloperidol and quetiapine for psychosis → "possible NMS"
- Propofol for sedation → intubated
- Magnesium sulfate and IV fluids

TREATMENT: GABA AGONISTS

- 537 patients randomized to:
  - Chlordiazepoxide 50 mg IM q6h
  - Chlorpromazine 100 mg PO q6h
  - Hydroxyzine 100 mg IM q6h
  - Thiamine 100 mg IM q6h
  - Placebo

- Decreased dosages on subsequent days
• Benzodiazepines
  • No single benzodiazepine proven to be more efficacious than others
    – Some data short acting agents associated with higher incidence of seizure
  • Long acting BZD with active metabolite preferred (e.g. diazepam or chlordiazepoxide)

• Front-loading vs. symptom triggered
  • Front loading – rapid administration of long-acting agent until there is a significant improvement in symptoms
    – Can lead to over-sedation
    – Permits self-tapering
  • Typically titrated to the development of lid-lag

### Table: Comparison of Drug Efficacy

<table>
<thead>
<tr>
<th>DRUG</th>
<th>SZ</th>
<th>DT</th>
<th>DT + SZ</th>
<th>Any AWS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlordiazepoxide</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>9</td>
<td>4</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Placebo</td>
<td>8</td>
<td>7</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>Thiamine</td>
<td>7</td>
<td>4</td>
<td>0</td>
<td>11</td>
</tr>
</tbody>
</table>

FRONT-LOADING VS. SYMPTOM TRIGGERED

• Symptom triggered is administration of agent in response to symptoms/AWS score
  – Example: 10 mg diazepam given each time CIWA-Ar > 8

• Front-loading associated with
  – More rapid resolution of symptoms
  – Less need for additional medications
  – Less reliance on withdrawal scales

SYMPTOM TRIGGERED VS. STANDING ORAL BZD

• Evaluated in both patients with alcohol dependence at risk for withdrawal, and those in withdrawal

• Symptom triggered resulted in:
  – Decreased amount of BZD
  – Decreased duration of treatment
  – Similar rate of withdrawal complications


• Symptom triggered, titrating-bolus therapy decreases:
  – Duration of AWS
  – Medication requirements
  – Fewer days of mechanical ventilation*
  – Lower incidence of HCAP
  – Shorter ICU stay
BARBITURATES

• Potentially attractive given sub-group of individuals that don’t respond well to benzodiazepines

• Phenobarbital is most studied

• Primary complication is need for mechanical ventilation

PHENOBARBITAL FOR ACUTE ALCOHOL WITHDRAWAL: A PROSPECTIVE RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED STUDY

Jonathan I. Mellozzi, MD, George C. Czobor, MD, Beth S. Moyer, MD, Anne V. Hurley, MD, Eric S. Leffler, MD.

• Randomized to phenobarbital vs. placebo
  – All subjects received lorazepam based on symptom-triggered protocol
  – Continuous infusion used as part of protocol

• Phenobarb resulted in:
  – Less ICU admits: (28% vs. 8%; 95% CI 14-41%)
  – Less overall lorazepam
  – No change in outcome (LOS, intubation, Sz)


BENZOS VS. BARBS

• Few studies exist directly comparing these agents:
  – For mild withdrawal, no difference
  – One study revealed barbiturates more efficacious in severe withdrawal than BZD, but not consistently observed
### PROPOFOL

- GABA<sub>A</sub> agonist; NMDA antagonist
- Short functional half-life may result in return of AWS symptoms when infusion discontinued
- Tachyphylaxis occasionally reported

### PROPOFOL

- Additional potential drawbacks not unique to AWS treatment
  - Propofol infusion syndrome
  - Hypertriglyceridemia

### PROPOFOL

- Respiratory depression prompting intubation is common
- Propofol should not be used for treatment of AWS in non-intubated patients
**PROPOFOL**

- Stereo-selective agonist at GABA$_A$
- Limited animal data suggest possible benefit
- 3 human studies
  - Symptom triggered lorazepam + standing baclofen vs. placebo
  - Standing dose baclofen vs. diazepam
  - Prophylactic baclofen for patients at risk of developing AWS

**BACLOFEN**

- Baclofen better than placebo
- Single study comparing baclofen to diazepam had similar outcomes
  - Relatively low overall amount of BZD given
- Cochrane review concluded insufficient data on outcome or safety
PROTOCOLS

- Associated with less over/under-dosing of BZD
- Numerous protocols exist
  - Front-loading approach with increasing doses of BZD (e.g. diazepam)
  - Addition of phenobarbital if agitation not significantly improved

- Use of such protocols associated with:
  - Reduced mechanical ventilation
  - Possibly reduced nosocomial infections
  - Possibly shortened length of ICU stay


NON-GABA AGONIST THERAPY
SYMPATHOLYTICS

- AWS results in increased sympathetic output, including HTN and tachycardia
- Use of beta antagonists or centrally-acting $\alpha_2$ agonists can ameliorate these signs, thereby masking the severity of withdrawal
- Limited data exist; their use may be associated with:
  - Delayed diagnosis
  - Under-treatment

DEXMEDETOMIDINE

- Centrally-acting $\alpha_2$ agonist
  - Similar to IV clonidine
- Can result in sedation, decrease HR/BP
  - No anti-convulsant activity
- Most literature on dexmedetomidine (DEX) and AWS is uncontrolled case reports/series

Dexmedetomidine Alleviates Ethanol Withdrawal Symptoms in the Rat

- 60 Rats placed on 4 day binge of EtOH + vitamins
  - 2 died during binge from intoxication
- Randomized to receive saline or dexmedetomidine (DEX) at 10, 16, 22, and 39 hours after last drink
  - 3 mcg/kg, 10 mcg/kg, or 30 mcg/kg
- Assessed evidence of withdrawal
DEX IN RATS

- Withdrawal features noted in all rats

- U shaped response with regards to “sum score”
  - Rigidity, tremor, irritability

GROUP | SEIZURE
---|---
Control | 3
DEX 3 | 3
DEX 10 | 0
DEX 30 | 1


- Non-randomized, retrospective review of patients receiving DEX for AWS
- Data collected 24 hours before/after DEX infusion began
- Lorazepam based on standardized AWS scoring system
  - Haloperidol for agitation or hallucinations
DEXMEDETOMIDINE FOR AWS

- 20 subjects, mean age 45
- Mean infusion: 49.1h (95% CI 37-61h)
  - Mean dose was 0.53 mcg/kg/hr
  - Bolus infusion given for 5 patients
- Post infusion:
  - Mean ↓ in lorazepam: 32 mg/24h
  - Mean ↓ in haloperidol: 5.6 mg/24h

DEXMEDETOMIDINE FOR AWS

- Complications:
  - 9 second asystolic pause (n=1)
  - Endotracheal intubation (n=1)
- ↓ in amount of drug administered should be expected during the second 24 hour period if good control achieved up front

DEXMEDETOMIDINE: SUMMARY

- Data at this point is primarily limited to a small, non-randomized study and rat data
- Animal data equivocal, and not compared with BZD
- May have some role in the future, but...
  - Dangerous for monotherapy
  - Role in combination therapy not yet established
ANTICONVULSANTS

CARBAMAZEPINE

• Limited data for use in out-patient treatment of mild AWS
  – Adverse events (nausea, ataxia, pruritus) commonly result in discontinuation (up to 50%)  
• Meta-analysis of 7 studies vs. BZD
  – Reduction in CIWA-Ar
  – Not superior for preventing W/D seizures
  – Possibly worse than BZD for preventing DT’s

GABAPENTIN

• Theoretical benefit based on structure
• Minimal data to suggest decrease CIWA-Ar in mild withdrawal
  – May be associated with ↓ probability of resuming EtOH early (but not late) during out-patient treatment
• No benefit in severe withdrawal
TOPIRAMATE

• Theoretical benefit due to:
  – Suppress glutamatergic input
  – Facilitate GABA mediated inhibitory impulse

• Rodent study demonstrated topiramate’s ability to attenuate withdrawal signs

• Human studies failed to demonstrate benefit

VALPROIC ACID

• Theoretical benefit due to
  – Increased GABA activity
  – Little abuse potential
  – Insignificant interaction with EtOH
  – Beneficial for several concurrent psychiatric diseases

• Data limited to 2 small, RCTs and several unblinded studies with standing VPA

VALPROIC ACID

• VPA may have some small benefit in mild-moderate withdrawal
  – Benefits are very minimal
  – Unclear if any clinical significance

• No benefit in severe withdrawal

• Safety unknown as most studies had exclusionary criteria not representative of most AWS populations

• No role at present
**ANTICONVULSANT VS. PLACEBO: META-ANALYSIS**

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>RELATIVE RISK (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Seizure</td>
<td>0.61 (0.31-1.2)</td>
</tr>
<tr>
<td>Adverse Event</td>
<td></td>
</tr>
<tr>
<td>Severe, life-threatening</td>
<td>2.98 (0.33-17.24)</td>
</tr>
<tr>
<td>Delirium</td>
<td>0.88 (0.23-3.42)</td>
</tr>
</tbody>
</table>

**ANTIPSYCHOTICS**

- Typical antipsychotics with D<sub>2</sub> receptor antagonism
- Hallucinations common with AWS
  - D<sub>2</sub> receptor antagonism useful for hallucinations due to other etiologies
- Few objective data evaluating their use

**Comparative Evaluation of Treatments of Alcohol Withdrawal Syndromes**

- 49 patients, randomized to:
  - Promazine (n=13)
  - Paraldehyde + chloral hydrate (n=12)
  - Ethanol (n=12)
  - Chlordiazepoxide (n=12)

- 23 developed DT's, including 12/13 treated with promazine
  - 2 deaths
Double-blind study of cyamemazine and diazepam in the alcohol withdrawal syndrome

- Randomized patients with CIWA-Ar between 10-30 to receive q1h PO drug
  - Cyamemazine 50 mg (n=45) vs. diazepam 10 mg (n=44) with subsequent taper
  - 26 subjects excluded 20 in incomplete data

- Similar % of patients with CIWA-Ar ≤ 5

<table>
<thead>
<tr>
<th></th>
<th>CYAMEMAZINE (n=43)</th>
<th>DIAZEPAM (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic failure</td>
<td>4 (9.1%)</td>
<td>1 (2.3%)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>19 subjects, 34 events</td>
<td>15 subjects, 24 events</td>
</tr>
<tr>
<td>Serious withdrawal</td>
<td>4 (9.1%)</td>
<td>1 (2.3%)</td>
</tr>
</tbody>
</table>

GABA AGONISTS VS. ANTIPSYCHOTICS: META-ANALYSIS

- Relative risk of death with antipsychotics alone 6.6 (95% CI 1.2-34.7)

- Comparing GABAergic drugs with antipsychotics, antipsychotics with:
  - Prolonged times of delirium
  - Longer time until adequately sedated

- No placebo-controlled RCTs evaluating antipsychotics with benzodiazepines
ANTIPSYCHOTICS

- Potential for adverse events:
  - Lower seizure threshold
  - Impair heat dissipation
  - Under-treat with GABA agonists
- No role for routine management
- May have role in select patient with concurrent psychiatric illness (psychosis)

MISCELLANEOUS AGENTS

KETAMINE

- Non-competitive NMDA receptor antagonist
- Pain literature shows doses of 0.1-0.5 mg/kg/hr well-tolerated
- Rodent data demonstrating reduced severity of AWS
KETAMINE

- Small, non-randomized human case series with continuous infusion of low-dose ketamine demonstrating:
  - Less BZD requirements than otherwise expected
  - Shorter lengths of ICU stay

SUMMARY

- GABA agonists remain first-line therapy for treatment of AWS
  - Benzodiazepines first-line but some individuals may require barbiturates

- Aggressive front-loading, symptom triggered approach preferred over continuous infusions or standing doses

SUMMARY (CONT.)

- No role for routine use of antipsychotics, anticonvulsants, and clonidine, β antagonists

- Ketamine appears to be a potential novel agent
  - Further studies needed before routine administration
QUESTIONS

THANK YOU!

REFERENCES


REFERENCES (CONT.)

REFERENCES


