The Treatment of Acute Alcohol Withdrawal

General Internal Medicine Grand Rounds
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Pharmacology

- Ethanol
- Benzodiazepines
- Chlormethiazole
- Barbiturates
- Propofol
- Anticonvulsants (Carbamazepine)
- Baclofen
- Antipsychotics
- β Blockers
- Clonidine
- Dexmedetomidine
Ethanol

- Short half life
- Narrow therapeutic index
- Gastric irritation
- Risk of metabolic derangements
- Risk of Wernicke-Korsakoff
- Poor surgical healing
- Expensive
- Ethical issues
Benzodiazepines

• 1969 Kaim article
  – 537 alcoholics
  – Double blind
  – Chlordiazepoxide, chlorpromazine, hydroxyzine, thiamine

Benzodiazepines

- Potentiate binding of GABA to GABA-A receptor

- Avoid IM for chlordiazepoxide and diazepam
  - Slowly & erratically absorbed

- Long vs Short half life
  - Seizures after cessation of short acting (oxazepam)
Benzodiazepines

- Chlordiazepoxide & Diazepam:
  - Oxidation
  - Glucuronidation
  - P450

- Lorazepam & Oxazepam:
  - Glucuronidation
Benzodiazepines

• Chlordiazepoxide & Diazepam:
  Oxidation \[ \text{P450} \] \rightarrow \text{Glucuronidation} 

• Lorazepam & Oxazepam:
  \text{Glucuronidation}
Benzodiazepines

Elderly & Severe Liver Disease

• **Chlordiazepoxide & Diazepam:**
  - Increased terminal elimination half-life
  - Increased volume of distribution
  - Greater accumulation of metabolites

• **Lorazepam & Oxazepam:**
  ➞ Preferred in Elderly & Severe Liver Disease
Chlormethiazole

- Sedative, hypnotic & anti-convulsant
- Enhances GABA-A
- Short ½ Life
- Only available in Europe
Chlormethiazole

- Equivalent to chlordiazepoxide

- Risk respiratory depression & cardiopulmonary collapse
  - Case reports of death in overdose

- Need to taper over 1 week

- Avoid as first line agent
Barbiturates

- Bind to GABA-A receptor
  (Inhibitory)

- Inhibit Glutamate receptors
  (Stimulatory)

- Risks:
  - Narrow therapeutic window
  - Tachycardia
  - Delirium & coma
Barbiturates

• Few controlled studies

• Avoid as first line, but...

• ? Add when refractory to massive benzodiazepine doses
  – act on different site of GABA-A receptor
Propofol

• Stimulates GABA-A receptor
• Inhibits glutamate receptors

• Need to intubate
Propofol

• Avoid as first line
• Can add when refractory to massive benzodiazepine doses

• Act on different site of GABA-A receptor
  -? augment benzo effect
Antipsychotics

- Few controlled studies

- ? Adjunct to benzodiazepines

- Lower seizure threshold
Beta Blockers

- Not recommended alone
- Studied in combination with benzos
Beta Blockers

• Evidence of increased:
  – Hallucinations
  – Delirium tremens
  – Seizures

• Make vitals look pretty…
  – mask early symptoms of withdrawal
• Inna Salum Study in Sweden (1972)
  – 1956 - 1961
  – 1,907 encounters
  – Men only

Vitals

• Fever

• **Tachycardia**

Vitals

• Hypertension

Clonidine

• $\alpha$-2 agonist

• Makes vitals look pretty…
  – masks sympathetic hyperactivity

• Evidence of increased:
  – Hallucinations
  – Seizures
Dexmedetomidine

• Selective central $\alpha$-2 agonist
  – Anxiolytic
  – Sedation
  – No respiratory depression

• Other Indications:
  – Non-intubated procedures
  – Critically ill mechanically ventilated patients

• Makes vital signs look pretty

• Studies in progress
Anticonvulsants

- Malcolm 2002
  - 136 Outpatients
  - Mild-moderate withdrawal
  - Compared Lorazepam to Carbamazepine
  - Outcomes:
    - Equal efficacy in decreasing withdrawal
    - Carbamazepine treated patients drank later and drank less

Anticonvulsants

- Malcolm 2002

Anticonvulsants

- **Other Benefits**
  - No abuse potential
  - No sedation

- **Hematologic & Hepatic toxicities**
  - Not observed in short detox protocols
Baclofen

• Selective GABA-B receptor agonist

• Mice studies:
  – Reduce withdrawal symptoms
  – Decrease craving
  – Decrease amount of EtOH consumed
  – Prevent sensitization to EtOH stimulant effects
Baclofen

• Addolorato (2006) Baclofen vs Diazepam
  – 37 subjects
  – Not blinded
  – “Moderate-Severe” EtOH withdrawal (Cl WA > 10)
  – Excluded DTs and hallucinosis

…..Similar decrease in Cl WA scores

Baclofen

• Lyon (2011) Baclofen vs. Placebo
  – 31 inpatients
  – Randomized, double-blind
  – All patients on oral Lorazepam for AWS

....reduced dose of lorazepam needed
  - but didn’t look at withdrawal outcomes

Baclofen

• Addolorato (2002) **Baclofen vs. Placebo**
  – 39 subjects
  – Randomized, double-blind
  – Significant dropout: 15% Baclofen
    42% Placebo

...Remained abstinent at 1 month:
  • Baclofen: 14/17 (70%)
  • Placebo 4/11 (21%)

Baclofen

• Garbutt (2010) Baclofen vs Placebo
  – 80 subjects
  – Randomized, double-blind
  – 12 week follow-up

...decreased anxiety in baclofen arm &

No difference in:
  • heavy drinking days
  • Days abstinent
  • Time to first drink
  • Time to relapse to heavy drinking

3 Approaches to Treatment

- Fixed-Schedule
- Front-Loading
- Symptom-Triggered
Fixed-Schedule

• Example:

Chlordiazepoxide 50 mg PO Q6 hr x 4 doses
then, 25 mg PO Q6 hr x 8 doses

(occasionally have the option of symptom-guided treatment in addition)
Fixed-Schedule

• Disadvantage:
  – Under or over dosing a patient
  – 60% of patients may require no treatment
  – Increased Length of Stay

• Advantage:
  – Prevents kindling
  – Prevents seizures
  – Can be used in medically ill patients
Kindling

• 1969 – Goddard, McIntyre & Leech
  – Electrical stimulation to animals

• Alcohol withdrawal:
  – **Repeated episodes of withdrawal develop:**
    • Progressively shorter duration of time b/w last drink & onset of symptoms
    • Progressively more severe symptoms
Kindling

- Ulrichsen 1995:

  - **Control**: (80 rats)
    

  - **Diazepam Treated Group**: (80 rats)
    

withdrawal episodes 10-13

X = Intoxication x 2 days

- = withdrawal x 5 days

- = withdrawal x 5 days (Treated with Diazepam)
Kindling

• Ulrichsen 1995: Rat study

Kindling

- **Risk of severe withdrawal:**
  - Hx seizures
    - …risk doubles (46% vs 20%)
  - Hx > 4 prior withdrawal episodes
    - …risk > triples (59% vs 17%)

Front-Loading

• **Examples:**
  - Diazepam 20 mg PO Q1 hr
  - Diazepam 20 mg IV Q10 min
  ...until AWS controlled or patient lightly sedated

• **First described by:**
  Addiction Research Foundation Clinical Institute
  -Toronto
  -used Barbiturates, and then Diazepam
Front-Loading

• Long acting benzodiazepine preferred (self taper)

• Advantages:
  – Rapidly controls withdrawal symptoms
  – Less risk of drug-seeking behavior
  – Can be used if history of prior seizures
  – Can be used in critically ill
  – Prevents kindling
Front-Loading

- **Gold (2007)**
  - 95 Subjects
  - Retrospective
  - Evaluated:
    - Intermittent bolus diazepam (pre-guideline)
    - Escalating doses of diazepam (post-guideline)
  - Critically ill AWS
  - Post-guideline: Front loaded based on a symptom scale and sedation scale
  - Phenobarbital or Propofol if resistant to massive doses of benzodiazepines

Bellevue Protocol (Lewis Nelson, MD)

- Notify Medical Toxicology service via PCC (212-POISONS)

- Diazepam 10 mg IV. If inadequate response, then immediately escalate.

- Diazepam 20 mg IV. May be repeated up to three times every 5-10 minutes PRN within one hour, then immediately escalate.

- Diazepam 40 mg IV. May be repeated up to three times every 5-10 minutes PRN within one hour, then immediately escalate.

- Diazepam 80 mg IV. May be repeated up to three times every 5-10 minutes PRN within one hour, then immediately escalate.

- Diazepam 100 mg IV. May be repeated every 5-10 minutes PRN until RASS 0 to -2 for 1 hour. If not reaching goal, escalate.

- Consider prophylactic use of chlordiazepoxide PO before AWS begins, or if AWS is very mild or easily controlled with Diazepam 10 mg IV.

- Consider intubation and propofol 25 mcg/kg/min IV with titration.

- Consult Medical Toxicology or ICU Fellow prior to decision to escalate.

- Avoid deep sedation and intubation. If not possible or practical, advance.

- Resistant Alcohol Withdrawal (RAW): Diazepam 200 mg in the initial 3 hours or Diazepam 400 mg in the first 8 hours. Diazepam ≥ 40 mg per dose for control. If RAW, add Phenobarbital (65-130 mg IV over 5 min q 30 min (slow onset), up to a total of 390 mg) and continue diazepam dosing/escalation.
Front-Loading

Bellevue Protocol

(Lewis Nelson, MD)

- Control patient’s behavior for 1 hour at RASS 0 to -2

Richmond Agitation Sedation Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>+4</td>
<td>Combative</td>
<td>Overtly combative, violent, immediate danger to staff</td>
</tr>
<tr>
<td>+3</td>
<td>Very agitated</td>
<td>Pulls or removes tube(s) or catheter(s); aggressive</td>
</tr>
<tr>
<td>+2</td>
<td>Agitated</td>
<td>Frequent non-purposeful movement, fights ventilator</td>
</tr>
<tr>
<td>+1</td>
<td>Restless</td>
<td>Anxious, apprehensive, but movements not aggressive</td>
</tr>
<tr>
<td>0</td>
<td>Alert and calm</td>
<td>Alert and calm</td>
</tr>
<tr>
<td>-1</td>
<td>Drowsy</td>
<td>Not fully alert, but has sustained awakening (eye-opening/eye contact) to voice (&gt;10 sec)</td>
</tr>
<tr>
<td>-2</td>
<td>Light sedation</td>
<td>Briefly awakens with eye contact to voice (&lt;10 sec)</td>
</tr>
<tr>
<td>-3</td>
<td>Moderate sedation</td>
<td>Movement or eye opening to voice (but no eye contact)</td>
</tr>
<tr>
<td>-4</td>
<td>Deep sedation</td>
<td>No response to voice. movement or eye opening to physical stimulation</td>
</tr>
<tr>
<td>-5</td>
<td>Unarousable</td>
<td>No response to voice or physical stimulation</td>
</tr>
</tbody>
</table>


- Propofol – primary sedative in intubated patients (in addition to diazepam)
Ativan Drips

• **NOT** Front-Loading

• **Why they’re bad:**
  - Over-sedation $\rightarrow$ ventilator $\rightarrow$ pneumonia
  - Often no assessment b/w dosing intervals
  - Increased risk of delirium 2/2 toxic benzo doses
  - Increased length of stay
  - Increased risk of debility due to prolonged sedation & bed rest
  - Increased cost ($50,335 for 25 hr midazolam)
Ativan Drips

- Propylene glycol toxicity:
  - Diluent
  - IV form of Lorazepam
  - Risk of toxicity when infusion rate $> 6$ mg/hr
  - Assoc w/: Lactic Acidosis
    - Osmolar gap
    - Renal Failure
Symptom-Triggered

• **Definition:**
  - Meds given when symptoms exceed a threshold
  - Different doses depending on degree of symptoms

• **It is not:**
  - Informal PRN orders:
    Diazepam 10 mg PO Q4 hr PRN for “EtOH withdrawal”

• **Not recommended alone for seizures**
Symptom-Triggered

• Gross et al. 1973
  – TSA (Total Severity Assessment)
    • 30 variables
  – SSA (Selected Severity Assessment)
    • 11 variables

• Most Scales:
  – Developed/tested in detox units
  – Extremely detailed
  – Burdensome to nursing staff
  – Poorly validated
Symptom-Triggered

• **CIWA-A** *(Clinical Institute Withdrawal Assessment for Alcohol)*
  - 1981
  - Addiction Research Foundation Clinical Institute (Toronto)
  - Research tool...quantify severity of withdrawal
  - Validated by comparing nursing & physician scores

• **CIWA-A**
  - Could be used to guide pharmacologic treatment

• **CIWA-Ar** *(Clinical Institute Withdrawal Assessment for Alcohol)*
  - 1989
  - 10 signs/symptoms *(No vital signs)*
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and Vomiting</td>
<td>Ask &quot;Do you feel sick to your stomach? Have you vomited?&quot; Observation.</td>
</tr>
<tr>
<td>Tremor</td>
<td>Arms extended and fingers spread apart. Observation.</td>
</tr>
<tr>
<td>Auditory Disturbances</td>
<td>Ask &quot;Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?&quot; Observation.</td>
</tr>
<tr>
<td>Tactile Disturbances</td>
<td>Ask &quot;Have you any itching, pins and needles sensations, any burning, any numbness, or do you feel bugs crawling on or under your skin?&quot; Observation.</td>
</tr>
<tr>
<td>Paroxysmal Sweats</td>
<td>Observation. 0 no sweat visible, 1 barely perceptible sweating, palms moist, 2 beads of sweat obvious on forehead, 3 drenching sweats.</td>
</tr>
<tr>
<td>Visual Disturbances</td>
<td>Ask &quot;Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?&quot; Observation.</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Ask &quot;Do you feel nervous?&quot; Observation. 0 no anxiety, at ease, 1 mild anxious, 2 moderately anxious, or guarded, so anxiety is inferred, 3 equivalent to acute panic states as seen in severe delirium or acute schizophrenic reactions.</td>
</tr>
<tr>
<td>Agitation</td>
<td>Observation. 0 normal activity, 1 somewhat more than normal activity, 2 moderately fidgety and restless, 3 pacing back and forth during most of the interview, or constantly thrashes about.</td>
</tr>
<tr>
<td>Headache, Fullness in Head</td>
<td>Ask &quot;Does your head feel different? Does it feel like there is a band around your head? Do not rate for dizziness or lightheadedness. Otherwise, rate severity.</td>
</tr>
<tr>
<td>Orientation and Clouding of Sensorium</td>
<td>Ask &quot;What day is this? Where are you? Who am I? 0 oriented and can do serial additions, 1 cannot do serial additions or is uncertain about date, 2 disoriented for date by no more than 2 calendar days, 3 disoriented for date by more than 2 calendar days, 4 disoriented for place or person.</td>
</tr>
</tbody>
</table>

Symptom-Triggered

CI WA-Ar

- Nausea/vomiting
- Tremor
- Paroxysmal Sweats
- Anxiety
- Agitation
- Headache, Fullness in head
- Tactile Disturbances
- Auditory Disturbances
- Visual Disturbances
- Orientation & Clouding of Sensorium
Symptom-Triggered

• CIWA-Ar Example:
  – Assess CIWA-Ar Q2 hour
  – Chlordiazepoxide 50 mg for CIWA-Ar ≥ 10
  – When CIWA-Ar < 10, reassess Q4 hour
Symptom-Triggered

- 4 CIWA-Ar studies:
  - Saitz 1994
  - Daeppen 2002
  - Jaeger 2001
  - Weaver 2006
Symptom-Triggered

• **Saitz 1994**
  - Chlordiazepoxide Fixed taper Q6 hr x 12 doses
    AND Chlordiazepoxide Q1hr if CIWA-Ar > 8
  - Placebo Fixed taper Q6 hr x 12 doses
    AND Chlordiazepoxide Q1hr if CIWA-Ar > 8

• 101 patients
• Randomized, double blind controlled
• Inpatient detox unit

Symptom-Triggered

• Saitz 1994

• Exclusions:
  • History of seizures
  • Medical or Psychiatric illness requiring hospitalization
  • Unable to take oral meds
  • Current use or withdrawal of other drugs

• Subjects that developed DTs:
  • Transferred to ICU (subsequent care not in study)

• < 30% had prior history DTs or Hallucinations

Symptom-Triggered

• Saitz 1994
  - Similar efficacy in reducing alcohol withdrawal symptoms

Symptom-Triggered

• **Daeppen 2002**
  
  ➢ Oxazepam Fixed taper Q6 hr x 12 doses AND Oxazepam Q30 min if CIWA-Ar > 8
  
  ➢ **Placebo** Fixed taper Q6 hr x 12 doses AND Oxazepam Q30 min if CIWA-Ar > 8

• 117 patients
• Randomized, double blind controlled
• 12 bed alcohol inpatient treatment program

Symptom-Triggered

• Daeppen 2002

• Exclusions:
  • Last EtOH drink > 72 hours prior
  • Daily use of meds to treat EtOH w/d in prior 1 month
  • Major cognitive, psychiatric or medical comorbidity
  • Opiate or stimulant dependency

• < 20% had prior history DTs or Seizure

• Withdrawal Complications:

<table>
<thead>
<tr>
<th></th>
<th>Seizures</th>
<th>Delirium Tremens</th>
<th>Hallucinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed-Dose</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Symptom-Triggered</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Symptom-Triggered

• **Daeppen 2002**

• Required Treatment: 100% Fixed-Schedule

39% Symptom-Triggered

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**Mean Oxazepam Dose (mg)**

- **Fixed Dose**: 231 mg
- **Symptom Triggered**: 37 mg

**Mean Duration of Treatment (Hours)**

- **Fixed Dose**: 63 hours
- **Symptom Triggered**: 20 hours

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Symptom-Triggered

• Jaeger 2001
  – Retrospective, Mayo Clinic
  – CIWA-Ar vs Prior Usual Care
  – Prior Usual Care = fixed dose protocol or PRN based on discretion of staff
  – Nurses trained in CIWA
  – Exclusions:
    • Hx seizures
    • Patients admitted to ICU

Symptom-Triggered

- Jaeger 2001
  - No difference in Length of Treatment
  - Decreased risk of DT with CIWA-Ar

Symptom-Triggered

• Weaver 2006
  • Goal: evaluate comorbid medical illness
    - Lorazepam Fixed taper x 4 days
      AND Lorazepam Q1 hour if CIWA-Ar > 30
    - Lorazepam Q 4 hour if CIWA-Ar > 6 (Q1 hr if > 30)
  • 183 patients
  • Hospital general medical floors
  • Quasi-randomized by nursing floor

Symptom-Triggered

• Weaver 2006
  • Most common comorbid diagnoses:
    • Pancreatitis, pneumonia, cellulitis, GI bleed, chest pain
    • ….but not clear what % of overall patients or the % in each treatment arm had a comorbid illness

• Exclusions:
  • Confusion
  • Chronic sedative-hypnotics
  • Patients admitted to ICU

Symptom-Triggered

• Weaver 2006

• Symptom-triggered:
  • Required less overall dose of medication
  • Incurred twice as many protocol errors
    – Frequency of assessments
    – Dispensing incorrect lorazepam dose based on CIWA-Ar
    – Giving scheduled lorazepam in addition to symptom-triggered

Symptom-Triggered

- CI WA-Ar
  - Never been compared to another symptom-triggered scale
  - No standardization of a drug dose to the scale
  - No standardization of nursing assessment frequency
  - Very limited studies in medical/trauma pts
  - Most studies include mild-moderate withdrawal
  - Usually patients excluded if active withdrawal
  - Often patients excluded if history seizures
Symptom-Triggered

- **SEWS**: Severity of Ethanol Withdrawal Scale
  - Thomas Beresford, MD @ VA
  - Goal to treat early withdrawal
  - Bimodal (Yes/No)
  - Includes vital signs
  - Does not include “Headache”
<table>
<thead>
<tr>
<th>Severity of Ethanol Withdrawal Scale</th>
<th>YES</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANXIETY</strong> (Do you feel that something bad is about to happen to you right now)?</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>NAUSEA and DRY HEAVES or VOMITING?</strong></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>SWEATING</strong> (includes moist palms, sweating now)?</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>TREMOR</strong> (with arms extended, eyes closed)?</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>AGITATION</strong> (fidgety, restless, pacing)?</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>ORIENTATION?</strong></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Name, place &amp; date: All three</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Any two only</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Any one only</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>HALLUCINATIONS</strong> (visual, tactile, olfactory, or gustatory)?</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>VITAL SIGNS?</strong> ANY of the following</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Pulse &gt; 110</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic BP &gt; 90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temp &gt; 99.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TOTAL SCORE =**

**TOTAL SCORE < 6:** Lower risk for withdrawal  
**TOTAL SCORE = or > 6:** Higher risk
Conclusions:

• **Benzodiazepines:** most evidence & clinical practice

• **In the ICU consider (in addition to Benzo):**
  - Propofol
  - Barbiturates
  - ? Dexmedetomidine

• **If Mask Withdrawal using:**
  - Beta-Blockers
  - Clonidine
  - ? Dexmedetomidine

• **Antipsychotics:** Lower seizure threshold

• **Promising:** Balcofen & Carbamazepine
Conclusions:

• Fixed-Schedule dosing should be limited
• Front-Loading promising
• Symptom-Triggered has:
  – decreased duration of detox
  – Reduced total dose of benzodiazepine
  – 60% of patients require no medications!
• Current gold standard CIWA-Ar is inadequate
  – No vital signs
  – Headache?
  – Burdensome for nurses & extremely detailed
• SEWS