# Management of Ethanol Withdrawal

# Ethanol
## Mechanisms of Action

- Stimulates GABA →downregulates receptor
- Inhibits NMDA →upregulates receptor

- Result in chronic use = excitatory state

# Ethanol Withdrawal Symptoms

**Timing of alcohol withdrawal syndromes**

| Syndrome | Clinical findings | Onset after last drink |
|---|---|---|
| Minor withdrawal | Tremulousness, mild anxiety, headache, diaphoresis, palpitations, anorexia, GI upset; Normal mental status | 6 to 36 hours |
| Seizures | Single or brief flurry of generalized, tonic-clonic seizures, short post-ictal period; Status epilepticus rare | 6 to 48 hours |
| Alcoholic hallucinosis | Visual, auditory, and/or tactile hallucinations with intact orientation and normal vital signs | 12 to 48 hours |
| Delirium tremens | Delirium, agitation, tachycardia, hypertension, fever, diaphoresis | 48 to 96 hours |

# Ethanol Withdrawal

## Management Principles

- alcohol withdrawal→seizures→DTs
- why in withdrawal? ($, GIB, AKA)
- address/treat other medical conditions
- administer thiamine
- medication
- if in DT's→admit to ICU, not easily reversible

# Benzodiazepines

- current "mainstay"
  - mechanism: $GABA_A$ agonists
- benefits
  - wide safety margin
  - anticonvulsant properties
  - no ceiling dose
  - practitioner comfort
  - *effective*

# Benzodiazepines

Benzodiazepines for AWS [5,6,8].

| Drug | Time to onset | Active metabolites? | Half-life (hrs) | Initial dose |
|---|---|---|---|---|
| Diazepam | 1–5 min IV | Yes | 43 ± 13 | 10–20 mg IV<br>10–20 mg PO |
| Lorazepam | 5–20 min IV | No | 14 ± 5 | 2–4 mg IV<br>2–4 mg PO |
| Midazolam | 2–5 min IM/IV | Yes | 2 ± 1 | 2–4 mg IM/IV |
| Oxazepam | 2–3 h PO | No | 8 ± 2 | 15–30 mg PO every 8 h |
| Chlordiazepoxide | 2–3 h PO | Yes | 10 ± 3 | 50–100 mg PO |

# Benzodiazpines

## Disadvantages

- do not agonize NMDA
- respiratory depression
  - despite continued withdrawal
- need for additional adjuncts

# Phenobarbital

- stimulates NMDA + $GABA_A$
- predictable peak CNS effect (20-30 minutes)
- relatively cheap
- no ceiling dose
- 3-4 days duration → no DC meds

# Phenobarbital
## Disadvantages

- practitioner unfamiliarity
  - Example: status epilepticus 20 mg/kg load
- Sharp ED→ not in pyxis (yet)

so takes 30-60 minutes to get from inpatient pharmacy

# Phenobarbital + Benzos

## Evidence

- intervention:
  - 10mg/kg IV phenobarbital + lorazepam CIWA
  - placebo + lorazepam CIWA
- results:
  - fewer ICU admissions (8% vs 25%)
  - no difference adverse events
    - decreased total lorazepam (26 mg vs 49 mg)

Rosenson et al. Phenobarbital for acute alcohol withdrawal: a prospective randomized double-blind placebo-controlled study. *J Emerg Med* 2013;44:592-8

# Phenobarbital + Benzos

## Evidence

- barbs alone or in combination with benzos
  - at least as effective
  - acceptable tolerability, safety
- adding phenobarbital to benzos reasonable
  - particularly to benzo-refractory pts

*J Critical Care* 2016; 32: 101-7

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Barbiturates for the treatment of alcohol withdrawal syndrome: A systematic review of clinical trials☆

Yoonsun Mo, MS, Pharm.D., BCPS, BCCCP [a,b,*], Michael C. Thomas, Pharm.D., BCPS, FCCP [a,1], George E. Karras Jr., MD, FCCM [b,2]

# Phenobarbital

## UCSD Proposed Dosing-conservative

- mild- 3 mg/kg
  - no response → repeat same dose
  - partial response → 1.5 mg/kg
- moderate/severe- 5 mg/kg
  - no response → repeat same dose
  - partial response → 3 mg/kg
- DT's 10 mg/kg
  - no response → repeat same dose
  - partial response → 5 mg/kg

*Round up to vial size

*Ideal body weight or adjusted body weight

# Use of Phenobarbital

- Average sized adult: 260mg IVPB
- Timing
  - wait 30 minutes prior to re-dosing (130mg increments)
- treatment goal
  - mild sedation, normalization of vitals
- serial dosing
  - can always add more

# Ethanol Withdrawal Treatment Summary

| | **Phenobarbital** | **Benzodiazepines** |
|---|---|---|
| Receptors | GABA, NMDA | GABA |
| Half life | Long (3-4Days) | Hours (variable) |
| DC meds req'd | No | Yes |

# Ketamine

- potential benefits:
  - NMDA antagonist
  - shorter acting so can give as infusion
  - maintenance of airway/breathing


Wong et al. Evaluation of adjunctive ketamine to benzodiazepines for management alcohol withdrawal syndrome. *Ann Pharmacother* 2015;49: 14-19 (0.3 mg/kg load; mg/kg/hr)

Shah et al. Adjunctive use of ketamine for benzodiazepine-resistant severe alcohol withdrawal: a retrospective evaluation. *J Med Tox* 2018;14: 229-36 (median initial 0.75mg/kg/hr)

# Ketamine in Delirium Tremens

- retrospective (total 63 patients)
- adjunct to benzos
- intervention:
  - potential bolus 0.3 mg/kg
  - infusion 0.15-0.3 mg/kg/hr
- endpoint: delirium resolution

Pizon et al. Adjunct ketamine use in the management of severe ethanol withdrawal. *Crit Care Med* 2018; 46: e768-71

## TABLE 2. Outcomes in Patients With Severe Ethanol Withdrawal Who Receive No Ketamine Versus Ketamine

| Outcomes | No Ketamine ($n = 29$) | Ketamine ($n = 34$) | $p$ |
|---|---|---|---|
| Mean ICU days | 11.2 | 5.7 | < 0.001 |
| Mean hospital days | 16.6 | 12.5 | 0.03 |
| Mean benzodiazepine dose in DE, mg | 2,525.1 | 1,508.5 | 0.02 |
| Dexmedetomidine use, *n* | 3 | 9 | 0.1 |
| Mean dexmedetomidine time, d | 2.33 | 1.77 | 0.4 |
| Intubations, *n* | 22 | 10 | < 0.001 |
| Mean benzodiazepine dose in DE equivalents, mg | 3,016.1 | 833.6 | 0.01 |
| Propofol use, *n* | | | 0.9 |
| Mean propofol time, d | 4.57 | 2.4 | 0.03 |

DE = diazepam equivalents.

# Ethanol Withdrawal Treatment

- Phenobarbital is safe +/- benzodiazepines
- Phenobarbital dosing:
  - 260mg IVPB
  - Wait at least 30 min for peak CNS effect
  - May repeat in 130mg increments (or use UCSD protocol 3-10mg/kg)
- If patient is discharged→no further medications required
- ICU for DTs→ consider ketamine infusion +GABA agonist