Alcohol, Sedative & Opioid Withdrawal – Challenging Patients

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Case 1

- 41-year-old businessman admitted for chest pain.
- Overnight he “ruled out”, when arriving to bring patient for stress echo he was found partially dressed and with one shoe on, tremulous, foot on the bed, swaying precariously.
  - He was diaphoretic.
  - Confused and disoriented
  - He’d pulled his IV out.

Case 1 continued

- Vitals: Overnight trend HR 80 bpm → 90’s, 100’s currently 120 beats-minute.
- BP 155/92 mmHg.
  - The patient is standing with one foot on the side of the bed, shaking, repetitively moving back/forth from his shoe to his shirt attempting to manipulate laces then buttons (back/forth without accomplishing anything).
  - He is visibly tremulous.
CNS Balance

- CNS output is a balance of excitation and inhibition. At baseline, though, we are excited...
- Excitatory neurons fire regularly while inhibitory neurons counteract this baseline excitation giving us a steady-state of balance.

Withdrawal Assessment -- assessing the 'fire'

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Prediction of Alcohol Withdrawal Severity

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Scoring PAWSS > 4 = HIGH RISK for moderate/severe w/d

- Score > 4 indicates potential for complicated withdrawal
- Prophylaxis and diligent attention to prevent progression of symptoms

Part C: Based on clinical evidence:

9. Was the patient’s blood alcohol level (BAL) on presentation ≥ 200? ________ (1 point each)
10. Is there evidence of increased autonomic activity?
   (e.g., HR > 120 bpm, tremor, sweating, agitation, nausea) ________

Total Score: ________

Notes: Maximum score = 10. This instrument is intended as a SCREENING TOOL. The greater the number of positive findings, the higher the risk for the development of AWS. A score > 5 suggests HIGH RISK for moderate to severe (complicated) AWS; prophylaxis and/or treatment may be indicated.

Put out the fire!

- GABAergic agents
  - Benzodiazepines
  - Phenobarbital
  - propofol

- Adjunctive Agents
  - Clonidine (adjunctive)
  - Neuroleptics (adjunctive)
  - Dexmedetomidine
  - Gabapentin (transition to treating dependence)

Case - back to our businessman… put out the fire!

- 41 year-old businessman – progression of anxiety, tachycardia, HTN, sweating, starting to hallucinate…?

Treating Alcohol Withdrawal - initial approach

Consider phenobarbital 65 mg PO every 12 hours x 2 doses as an alternative to BZD for initial management of CDA score ≥ 10:

- Patient high risk for development of complicated alcohol withdrawal [CDA ≥ 5]
- Yes
  - Place order for BZD as needed for CDA score ≥ 10
  - Yes
  - Evaluate CDA score
  - No
Decreasing Ethanol Level

- Alcohol withdrawal seizure "rum fit"
- Alcoholic tremulousness
- Tachycardia
- Hypertension
- Hyperthermia
- Tremor
- Diaphoresis
- Delirium tremens

Alcoholic hallucinosis

From Goldfranks: Chapter 70 Sedative-Hypnotic withdrawal

Phenobarbital Protocol for EtOH w/d part #1

- PHENOBARBITAL PROTOCOL:
  - Assess patient for withdrawal signs and symptoms using CIWA or other objective measurement.
  - 1.) for CIWA >15 select 65 mg of phenobarbital IV as first dose
  - 2.) Reassess in 10-15 min.
    - if symptoms improved but still present then redose at 65 mg.
    - If not improved dose at 130 mg and repeat q 15-30 minutes until relaxed
    - Clonidine adjunctively

- Goal: cessation of withdrawal symptoms without significant 'overshooting'. Ideal endpoint is a patient who is sleepy but still conversant with tremor markedly improved along with marked improvement in adrenergic signs and symptoms such as tachycardia, hypertension and diaphoresis.

Adjuvanct Meds - clonidine 0.1 mg 1-2 PO QID PRN

- Clonidine PO tabs and/or patch (0.1 mg- 0.3 mg/week)
  - Alpha2 agonist decreases norepinephrine outflow (decreases anxiety, adrenergic tone down)
  - Hold for HR < 55 bpm and SBP < 90 mmHg (MAP < 60 mmHg)

- Neuroleptics --NOT for patients with autonomic hyperactivity--
  - Haloperidol (1-5 mg PO/IV/IM every 4 hours PRN for delirium/hallucinations AFTER w/d attenuated (e.g. sleep patient paroxysms of 'flailing around/hallucinating' but autonomic hyperactivity clearly attenuated by GABAergic agents (primarily)
  - Olanzapine 12.5-25 mg PO q 8 hours PRN

GABA Transmission

- Benzodiazepine Receptor
- GABA Receptor
- Cl-
GABA stimulation causes inward flux of chloride resulting in hyperpolarization of the neuronal membrane which inhibits excitatory impulse propagation.

29-year-old Indian male is brought in by police after being found on the street. Two empty bottles of "mouthwash" are next to him. He is maintaining his airway, breath alcohol is difficult to obtain due to "compliance with breathalyzer". Blood alcohol returns at 440 mg/dL. Over the next two hours he wakes up. By 0400 he is becoming tremulous and he's moved from "special cares" to the main ED.

Case

- He's moved from "special cares" to the main ED. Bloodwork: K 2.9, HCO3 18, EtOH 280 mg/dL (4 hours apart).
- Several mg of IV lorazepam → increasingly tachycardic and tremulous → IV diazepam in 10 mg increments to 100 mg without significant improvement.
- Phenobarbital is given -260 mg IV then 120 mg increments 15 to 30 minutes until he is 'sleepy' and his HR and BP have 'normalized'.
- Additional 'supportive' (vitamins, IVF, electrolytes, additional labs/cultures...) initiated.

Principals of alcohol withdrawal Management

- 1.) Restore inhibitory tone to the central nervous system using long acting benzodiazepines or barbiturates.
- 2.) Identify and correct fluid, electrolyte and nutritional deficiencies.
- 3.) Evaluate for concurrent infection.
- 4.) Achieve goal 'inhibitory' target quickly.
Gabapentin and alcohol dependence...

Gabapentin Treatment for Alcohol Dependence: A Randomized Controlled Trial

Conclusions and Relevance

Gabapentin (particularly the 1800 mg dosage) was effective in treating alcohol dependence and relapse-related symptoms of insomnia, dysphoria and craving, with a favorable safety profile. Increased implementation of pharmacological treatment of alcohol dependence as primary care may be a major benefit of gabapentin as a treatment option for alcohol dependence.

Benzodiazepine Problems --CASE

A 30 year old man arrives to the emergency department stating that he has been taking 4-6 mg Etizolam (buying from non-medical sources) every day and that he wants to “detox”

- Further history is obtained: He has used 4-6 mg of etizolam every day for past 7 months. His last dose was 6 hours prior to arrival in the emergency department.
- He has no history of seizures, drinks EtOH once a month (6 standard shots) he has not experienced any symptoms of withdrawal in the past seven months.

Benzodiazepine Withdrawal

• Common Findings
  - Tremor
  - Myoclonic movements
  - Nausea/vomiting
  - Autonomic excitation
  - Craving

• Prolonged withdrawal
  - Periods weeks to month, irregular day to day: insomnia, perceptual disturbance, tremor, sensory hypersensitivity, anxiety

Benzodiazepine Withdrawal

• Factors for withdrawal
  - Dose
  - Duration of use
  - Duration of drug action
• Clinically significant withdrawal most likely
  - Daily low dose for 4-6 months
    - Daily high dose (2-3x upper limit of therapeutic) for more than 2-3 months.
• Timing of withdrawal
  - Short acting (lorazepam, oxazepam, triazolam, alprazolam, temazepam)
    - Onset within 24 hours, peak in 1-4 days. Seizure may occur at 2-3 days
    - Long acting: diazepam, chlordiazepoxide, clonazepam
    - Onset within 5 days, peak 1-9 days, seizures may occur up to 7 day
  - Comparison to alcohol withdrawal: onset within hours following last drink, risk of seizures highest in first 48 hours, alcohol withdrawal delirium may start 2-5 days after last drink
Benzodiazepine Dependence – taper (not my preference)

- Long acting benzodiazepine regimen fixed dose taper
  - Day 1: Chlordiazepoxide (Librium) 50mg or diazepam (Valium) 10-20 mg IV/PO QID
    • May give additional chlordiazepoxide 50mg PO or diazepam 10 mg IV/PO q2h pm between scheduled doses for uncontrolled alcohol withdrawal symptoms (CIWA ≥10)
  - Day 2 – chlordiazepoxide 25mg PO or diazepam 10 mg IV/PO qid
    • May give additional chlordiazepoxide 25mg PO or diazepam 10 mg IV/PO q2h pm between scheduled doses if uncontrolled withdrawal symptoms (CIWA ≥10).
  - Day 3 – Librium 25mg PO or diazepam 10 mg IV/PO qid
  - Day 4 – Librium 10mg PO or diazepam 5 mg IV/PO qid pm for continued withdrawal symptoms

Phenobarbital protocol

- Test dose then incremental dosing – PB has depot effect (very lipid soluble) and this dosing will allow for ‘auto titration’ as it slowly leaves the body

Classical Regimen (from Kawasaki et al prev page.)

- URMC Toxicology Protocol
  - Phenobarbital 130 mg PO x 1 (after w/d symptoms visibly attenuated)
  - Day 1) 130 mg PO q 4 hours x 6.
  - Day 2) 130 mg PO q 6 hours x 4.
  - Day 3) 130 mg PO q 8 hours x 3.
  - If any sedation hold dose. If dose held for 2 consecutive doses then d/c protocol.
  - Clonidine 0.1 mg PO QID PRN anxiety adjunctive to above protocol (with/without Catapres™ patch)

Opioid withdrawal in ED/Hospital

- A 19 year-old Male presents to the Emergency Department with a complaint of opioid withdrawal and he is requesting help with getting into treatment.
  - He reports using Vicodin™ and Percocet™ for several years with increasing doses until he started using Oxycontin™ tablets—and IR oxycodone, usually 30 mg tabs on average 300 mg total/day.
  - He states he’s been looking for a Suboxone™ program but hasn’t found anyone with open slots.
Case One continued

It has been over 24 hours since his last use of oxycodone. He has occasionally been able to buy Suboxone™ "...off the street..." but was unable to procure any this time.

Exam:
- **Vitals**: HR 110 bpm, BP 144/70 mmHg, temp 37.6 C
- **General**: The patient is mildly diaphoretic, very restless, and has quite a bit of tearing in his eyes. He has quite significant rhinorrhea.
- **HEENT**: Marked mydriasis.

Additional: You note that he yawns very prominently several times during the interview.

Detoxification

- **Options**:
  - A.) opioid agonists
  - B.) adjunctive meds
    - Clonidine
    - Antihistamines
    - Analgesics (non-opioid)
    - Benzodiazepines or baclofen
    - Ondansetron
    - Loperamide
    - Others?

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**Title 21 Code of Federal Regulations**

Section 1306.07 Administering or Dispensing of Narcotic Drugs

- A practitioner may administer or dispense directly (but not prescribe) a narcotic drug listed in any schedule to a narcotic dependent person for the purpose of maintenance or detoxification treatment if the practitioner meets both of the following conditions:
  - (1) The practitioner is separately registered with DEA as a narcotic treatment program.
  - (2) The practitioner is in compliance with DEA regulations regarding treatment qualifications, security, records, and the prescribed use of the drugs pursuant to the Act.

- Nothing in this section shall prohibit a physician who is not specifically registered to conduct a narcotic treatment program from administering (but not prescribing) narcotic drugs to a person for the purpose of relieving acute withdrawal symptoms when necessary while arrangements are being made for referral for treatment. Not more than one day’s medication may be administered to the person or for the person’s use at one time. Such emergency treatment may be carried out for not more than three days and may not be renewed or extended.

- This section is not intended to impose any limitations on a physician or authorized hospital staff to administer or dispense narcotic drugs in a hospital to maintain or detoxify a person as an incidental adjunct to medical or surgical treatment of conditions other than addiction, or to administer or dispense narcotic drugs to persons with intractable pain in which no relief or cure is possible or none has been found after reasonable efforts.

- A practitioner may administer or dispense (including prescribe) any Schedule II, III, IV, or V narcotic drug approved by the Food and Drug Administration specifically for use in maintenance or detoxification treatment to a narcotic dependent person if the practitioner complies with the requirements of § 1301.28 of this chapter.

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**Hospital & ED use exempt when medical issue present**

- In the ED or inpatient setting, an X-waiver is not required.
- Providers are administering or dispensing buprenorphine, not prescribing it for outpatient use.
- Physicians in a hospital or ED can treat acute withdrawal with buprenorphine or methadone while the patient is attempting to access treatment.
- The patient may not receive more than three days of administered methadone in the emergency department or hospital unless there is a concomitant acute medical or surgical condition requiring treatment.
- If a patient who is currently in a medication assisted treatment program their medication may be continued in the hospital, but they may not be discharged with a prescription.
- If the treating provider is X-waivered (able to prescribe buprenorphine for the treatment of opioid dependence) and they are able to link the patient to either their own clinic or another provider who also has X-waiver they can continue the buprenorphine (Suboxone™).
Opioid Withdrawal Treatment Regimens

- **Symptomatic Treatment**
  - **Clonidine 0.1 – 0.2 mg PO q4hr prn**
  - **Hold** for systolic BP < 100 mm Hg, pulse < 65 bpm
  - **Gabapentin 400-600 mg PO q6 hr prn**
  - **Antihistamines**
    - **Hydroxyzine 50 mg 1-2 PO QID PRN**
    - **Diphenhydramine 25-50 mg PO QID PRN**
      - **rhinorrhea, pruritis, also effective for nausea**
  - **Antiemetics**
    - **Ondansetron 8 mg PO (also an SL formulation if significant nausea/ inability to keep down) TID PRN**
  - **Sedatives**
    - **Valium 10mg IV or PO q6 hr prn**
      - **Hold** for sedation and/or disinhibition
    - **Zolpidem 5 mg PO or trazodone 50 mg PO qhs prn insomnia**
    - **Loperamide 4mg PO x 1 pm diarrhea, 2 mg after each subsequent stool (max 16 mg/day)**
    - **Olanzapine 5 mg IV or 10mg PO q8hr prn**
  - **NSAIDS**
    - **Ibuprofen 600 mg PO q4hr prn**
    - **Ketorolac 30 mg IV q6 hr prn**
    - **Acetaminophen 325-650 mg PO prn**

- **Methadone**
  - **Options for initial dose**
    - **20-30 mg PO**
      - **May repeat 10mg dose later that day if continued withdrawal**
    - **10 mg IM**

*If not in a medication assisted therapy program*

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Opioid Withdrawal Regimens

- **Buprenorphine**
  - **Day One**
    - **Take 2mg buprenorphine-naloxone sublingual tablet/film**
    - **Monitor** for opioid withdrawal symptoms over 1 hour (stomach cramps, nausea, muscle aches, yawning, stuffy nose)
    - **If no opioid withdrawal symptoms appear after 1 hour, administer one 8 mg buprenorphine-naloxone sublingual tablet/film**
  - **Day Two**
    - **8-16 mg buprenorphine-naloxone sublingual tablet/film**
    - **Next plan either link to treatment and maintenance regimen vs taper (3-7 days)**

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Buprenorphine Pharmacology

- **Buprenorphine is a partial mu receptor agonist**
  - **Kappa receptor antagonist**

PK: buprenorphine half-life 4-6 hours but metabolites (e.g. nor buprenorphine) have a very long duration of action T1/2 =

Peak analgesic effect = 4-6 hours

**Monitoring:**
- buprenorphine level
- nor buprenorphine
- buprenorphine glucuronide
- nor buprenorphine glucuronide
Opioid Pharmacology - a better opioid?

Full mu opioid agonists activate mu receptors. Increasing doses of full agonists produce increasing effects until a maximum effect is reached (the receptor is fully activated). morphine, heroin, methadone, oxycodone, hydromorphone, etc.

Dose Response - partial agonist and 'ceiling effect'

Agonist & Antagonist

Comparison of serum testosterone levels in 17 patients treated with buprenorphine, 37 patients treated with methadone, and 51 healthy controls.

Bliesner N et al. JCEM 2005;90:203-206

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Evidence for effectiveness

Case

• 31 year-old M with IVDU heroin and cocaine is hospitalized for fever and myalgias. Found to have endocarditis. Requires valve replacement and prolonged antibiotics.
• After surgery, and while on a fentanyl PCA, the CV surgery team contacts toxicology to help transition from fentanyl PCA and wean from opioids.
• Buprenorphine initiated 12 hours after PCA transitioned to off. 2/0.5 mg Suboxone™ started then 1 hour later 8/2 mg SL (continued SL BID)

The Heroin Blocker

• 42 year-old African-American Male presents to Suboxone™ clinic for an intake assessment.
• Long history of chemical dependency with primarily opioids (heroin and ‘street’ methadone) and cocaine.
• Prior exposure to ‘street’ buprenorphine through primarily Suboxone™ tabs being purchased when he cannot afford or cannot find heroin (5-8$/tab -8/2 mg Suboxone™ tabs).
• Describes purchasing an 8/2 mg Suboxone™ tab, several hours later coming into some money he purchases a “bundle” (10 bags) of heroin. Use of heroin completely blocked.

References