Evidence-Based Withdrawal Management of Alcohol and Opioid Use Disorders

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DISCLOSURES

Financial Interests:
1) Own Bonds for Pfizer, Inc. in IRA Account
2) Own Stock in GW Pharmaceuticals in IRA Account
3) Own Stock in Cortex Pharmaceuticals in IRA Account
4) Spousal Ownership of Stock Options/Bonds in Abbott Laboratories, Abbvie, and Hospira

Conflicts of Interest: Nothing to disclose

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Presentation will include discussion of off-label uses for various medications.

OBJECTIVES

1) How to disseminate the evidence that supports use of an alcohol withdrawal protocol and opioid withdrawal protocol for acute detoxification from these substances.

2) How initiation of substance-specific pharmacotherapy in the hospital prior to discharge can improve engagement in long-term, ongoing outpatient treatment for substance use disorders.

3) The FDA-approved pharmacotherapeutic treatment options to prevent relapse to opioids and/or alcohol.
UNDERSTANDING TREATMENT OF ALCOHOL WITHDRAWAL

• Incidence of Alcohol Withdrawal Syndrome
  • The incidence of any alcohol withdrawal symptoms in patients with severe alcohol use disorder in a treatment population is approximately 80%.1
  • Approximately 10%-15% of patients who develop alcohol withdrawal will develop Delirium Tremens without treatment.
  • The Goal of Hospital Management of Alcohol Withdrawal is Prevention of Delirium Tremens and other alcohol-associated complications.


PREVENTING WERNICKE’S ENCEPHALOPATHY AND KORSAKOFF’S PSYCHOSIS – ROLE OF THIAMINE

• Etiology of Wernicke's Encephalopathy and Korsakoff's Psychosis1
  • Intracellular Vitamin B1 Deficiency (Thiamine)
  • Leads to focal acidosis, increased neuronal glutamate, and neuronal cell death.
  • 90% of cases in industrialized countries are due to alcohol dependence.
  • Morbidity and Mortality of Wernicke's Encephalopathy
    • Wernicke's Encephalopathy associated with a 20% mortality.1
    • 75% of survivors left with permanent Brain Damage.1


PREVENTING WERNICKE’S ENCEPHALOPATHY AND KORSAKOFF’S PSYCHOSIS – ROLE OF THIAMINE

• People have proposed adding thiamine to alcoholic beverages but this would not prevent deficiency.
• Why is thiamine deficiency so common in patient’s with alcohol dependence?2
  • Alcohol inhibits gastrointestinal absorption of thiamine.
  • Alcohol metabolism prevents thiamin phosphorylation and incorporation into enzymes in the body tissues leading to an intracellular thiamine deficiency.

PREVENTING WERNICKE’S ENCEPHALOPATHY AND KORSAKOFF’S PSYCHOSIS – ROLE OF THIAMINE

• Recommendations:
  • All patients presenting to the emergency department with active alcohol dependence should receive an initial dose of parenteral thiamine (intravenous preferred), at least 100 mg, prior to giving carbohydrates.¹
  • Administration of glucose or carbohydrates in patients with thiamine deficiency could precipitate an encephalopathic crisis.
  • It is preferred that thiamine be administered as soon as possible (door to thiamine time) through data on exact timing is not currently available.
  • Patient’s admitted for detoxification without symptoms of Wernicke’s Encephalopathy should be continued on oral high dose, daily thiamine and encouraged to normalize their diet as quickly as possible.
  • In patient’s with Wernicke’s Encephalopathy, thiamine dose may need to be increased to doses as high as 500 mg three times per day.


BENZODIAZEPINES DISCOURAGED FOR ALCOHOL WITHDRAWAL?

The same Article from The Hospitalist News leading to numerous calls from colleagues wondering if we should “toss” the CIWA Protocol.

BENZODIAZEPINES DISCOURAGED?

WHAT IS THE DATA?

• In the study cited in the article, Dobrydnov et al studied Intrathecal and Oral clonidine vs diazepam for postoperative prophylaxes of alcohol withdrawal syndrome.¹
  • Prophylactic preoperative treatment with intrathecal or oral clonidine resulted in a significant reduction of postoperative alcohol withdrawal syndrome (AWS).
  • Strengths: Well Planned Randomized, Double Blinded, Placebo-controlled Study.
  • Weaknesses:
    • Small Number of Participants (45 total).
    • Only men were included.
    • Only inclusion criteria was daily alcohol consumption of >60 grams of pure ethanol (or 4.25 average drinks per day).
    • Groups NOT controlled for total alcohol consumption after inclusion.
      • For example, it is unclear if Group treated group consumed, on average, more ethanol than clonidine group.
    • Good correlation exists in literature regarding daily ethanol dose and severity of AWS symptoms.

**SYSTEMATIC REVIEWS**

- **Systematic Review of Prevention and Therapy of Alcohol Withdrawal in Intensive Care Units.**
  - Ungur, et al performed a Medline search and found 6 controlled trials for AWS prevention and 8 for AWS therapy in ICU's.
  - Prevention treatments studied as single agents included clonidine, ethanol, and benzodiazepines (BZO), while those studied in drug combinations included BZO, clonidine, clonazepam, and haloperidol.
  - All evaluated single agents and combinations found to be effective for AWS Prevention.
  - Clonidine was not recommended due to increased risk of respiratory distress.
  - Several agents were not studied in randomized trials as single therapy and phenoxybenzamine, clonidine, haloperidol, and benzodiazepines were not included in the systematic review.
  - All treatments found to be effective measured against placebo.
  - All treatment trials with historical controls found better outcomes with symptom-triggered BZO therapy than controls.
  - Overall recommendation by investigators is to use BZO therapy for prevention and AWS therapy using standardized, symptom-triggered protocol.


- **Amato, et al. performed a Cochrane Database Systematic Review of the efficacy and safety of pharmacological interventions for treatment of the AWS.**
  - Conclusions:
    - Benzodiazepines showed protective benefit against seizures when compared to placebo and potentially protective benefit on many outcomes when compared to antipsychotics.
    - Data regarding side effects were underreported.
    - Difficult to evaluate safety and efficacy versus other treatment options.
    - No definitive conclusions regarding safety and efficacy were possible due to heterogeneity of trials.
    - Results do not provide sufficient evidence in favor of anticonvulsants.
    - Not enough evidence in favor of safety and efficacy of baclofen was available as there was only one study considered.
    - Alpha-2 Agonist agents (clonidine and dexmedetomidine) were not evaluated in this systematic review.


- **Muzyk et al. studied the role of α2-agonists in the treatment of acute alcohol withdrawal in their systematic review.**
  - Studies primarily involved clonidine and dexmedetomidine.
  - Conclusion: The primary role for clonidine and dexmedetomidine are as adjunctive treatment to benzodiazepines.

Clomethiazole (also called chlormethiazole) is a sedative and hypnotic originally developed by Hoffmann-La Roche in the 1930s. The drug is used in treating and preventing symptoms of acute alcohol withdrawal.

Chlomethiazole acts as a positive allosteric modulator at the barbiturate/picrotoxin site of the GABA-A receptor. It works to enhance the action of the neurotransmitter GABA at this receptor.
INDIVIDUAL AGENTS

• Anticonvulsants
  • Gabapentin
    • A literature review demonstrates efficacy of Gabapentin for alcohol withdrawal treatment.
    • Seizures occur more often with use as monotherapy at doses less than 900 mg/day.
    • Use as monotherapy for mild alcohol withdrawal and outpatient detoxification may be possible though additional data still needed.
    • Studies demonstrate that gabapentin has a dose-dependent benefit to assist with maintenance of sobriety for alcohol if continued after alcohol detoxification:
      • Increases rates of complete abstinence
      • Associated with a decrease in heavy drinking days
      • Associated with a decrease in craving

• Anticonvulsants
  • Depakote and Carbamazepine have good data as adjunctive therapy to benzodiazepines for therapy of AWS symptoms.1,2
    • Pregabalin
      • Fog, et al studied pregabalin versus placebo using diazepam for rescue.1
      • Pregabalin was found to be safe but there was no evidence to support increased efficacy over placebo for treatment of AWS.

• Anticonvulsants
  • Levetiracetam
    • Richter, et al studied levetiracetam versus placebo using diazepam for rescue.
    • Data did not support an additional effect of levetiracetam on reduction of AWS symptoms.
  • Zonisamide
    • Rubin, et al studied zonisamide versus diazepam for AWS.
    • Both drugs reduced AWS symptoms but the decrease was more marked in zonisamide group which also experienced decreased craving.
**INDIVIDUAL AGENTS**

- **Apha-2 Agonists**
  - Studies demonstrate reductions in AWS symptoms with Clonidine and Dexmedetomidine but studies have not shown superiority/equivalency to benzodiazepines especially for severe AWS.\(^1\)
  - Probably best utilized as adjunctive prophylaxis therapy for AWS at this time.\(^1\)
  - Excellent Safety Profile for Clonidine

- **Potential Side Effects**
  - Hypotension
  - Bradycardia
  - Sedation (especially with dexmedetomidine)


**INDIVIDUAL AGENTS**

- **Novel Agents**
  - Baclofen
    - Cochrane database review demonstrated insufficient evidence to recommend the use of Baclofen for AWS.\(^1\)
    - At least one well conducted study demonstrated that Baclofen was associated with a significant reduction in the requirement for high-dose benzodiazepines and may be helpful as adjunctive therapy in the treatment of the AWS.\(^2\)
  - **Side Effects**
    - Seizures (lowers seizure threshold)
    - Confusion/Hallucinations (rare)
    - Drowsiness
    - Headaches
    - Insomnia


**INDIVIDUAL AGENTS**

- **Novel Agents**
  - Oxytocin
    - Rodent studies demonstrate that oxytocin inhibits neuroadaptation to and withdrawal from alcohol.
    - A recent study demonstrated that intranasal oxytocin may block alcohol withdrawal in human subjects.\(^1\)
    - Oxytocin may have advantages over benzodiazepines because it may reverse, rather than maintain, sedative-hypnotic tolerance.
    - Future studies will need to determine whether oxytocin reduces drinking in alcohol-dependent patients.

INDIVIDUAL AGENTS

- Novel Agents
  - Propofol
    - Numerous case reports and case series presentations demonstrate the efficacy of propofol for patients with refractory delirium tremens despite high-dose benzodiazepines.1-3
    - Side effects present widespread use outside the Intensive Care Unit Setting.
      - Significant respiratory depression/sedation requiring endotracheal intubation.
      - Hypotension
      - Acute pancreatitis
      - Increased risk of infections and metabolic acidosis.
      - Propofol infusion syndrome (rare with long-term infusion).
      - Cardiac failure
      - Renal failure
      - Metabolic Acidosis
      - Rhabdomyolysis


SUMMARY REGARDING ALCOHOL WITHDRAWAL MANAGEMENT

- Benzodiazepines remain the mainstay of treatment for alcohol withdrawal to prevent development of more severe complications including seizures and delirium tremens.
  - Numerous studies support use of Symptom-Triggered Therapy (utilizing the CIWA-Ar Scale) over scheduled dose benzodiazepine.
  - Benzodiazepines have dose-dependent side effects including sedative associated delirium, confusion, and respiratory depression.
  - Use of adjuvant medications to decrease the burden of benzodiazepines for alcohol withdrawal syndrome is supported by numerous studies.
  - Gabapentin demonstrates excellent efficacy with minimal side effects.
  - Alpha-2 Agonist Agents also safe and decrease symptoms.

PHARMACOLOGY FOR MAINTENANCE OF SOBRIETY FROM ALCOHOL - NALTREXONE

- FDA-Approved Pharmacology for Alcohol Dependence
  - Naltrexone
    - Mechanism of Action: Mu-Opioid Antagonism
    - Available as an oral tablet that the patient takes once per day or an extended-release intramuscular injection every four weeks.
    - Alcohol ingestion releases endogenous endorphins that may account for alcohol's addictive potential.1
    - Overall Compliance with oral naltrexone is poor.
    - Efficacy to improve outcomes in alcohol use disorder greatest in combination with psychotherapy and utilized best to minimize heavy drinking days.2
    - Potential Side-Effects include dose-dependent hepatotoxicity.


### PHARMACOLOGY FOR MAINTENANCE OF SOBRIETY FROM ALCOHOL - NALTREXONE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Treatment Method</th>
<th>( \Delta ) Difference in Effects Between Treatment Groups</th>
<th>( \Delta ) Naltrexone  vs Placebo</th>
<th>( \Delta ) Placebo  vs Treatment</th>
<th>( % ) Change in Effects</th>
<th>Conclusion</th>
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<td>NSG</td>
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### PHARMACOLOGY FOR MAINTENANCE OF SOBRIETY FROM ALCOHOL - ACAMPROSATE

**FDA-Approved Pharmacology for Alcohol Dependence**

**Acamprosate**

- **Mechanism of Action:** Not well described and somewhat controversial.
- **Theoretical:** Promotes a balance between the excitatory and inhibitory neurotransmitters.  
- **Available:** As a 333 mg oral tablet that is taken two tablets three times per day.
- **Efficacy:** For relapse prevention demonstrated in over 25 randomized, double-blind, placebo-controlled trials.  
- **Side Effects:** Include gastrointestinal side effects (diarrhea, nausea, vomiting) and pruritus.  


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### PHARMACOLOGY FOR MAINTENANCE OF SOBRIETY FROM ALCOHOL - DISULFIRAM

**FDA-Approved Pharmacology for Alcohol Dependence**

**Disulfiram**

- **Mechanism of Action:** Blocks the enzymes acetaldehyde dehydrogenase leading to accumulation acetaldehyde with alcohol consumption.
- **Lead to:** Disulfiram-ethanol reaction (DER) with tachycardia, flushing, nausea, and vomiting.
- **Prevent relapse:** By creating severe discomfort if the patient drinks alcohol but requires compliance with medication.
- **Efficacy:** For relapse prevention demonstrated in multiple studies but does not decrease cravings.  
- **Side Effects:** Include hepatotoxicity, peripheral neuropathy, and gastrointestinal side effects (diarrhea, nausea, vomiting).  

PHARMACOLOGY FOR MAINTENANCE OF SOBRIETY FROM ALCOHOL – OTHER OPTIONS

• Non-FDA-Approved Pharmacology for Alcohol Dependence
  • Anti-epileptic Medications
    • Gabapentin
    • Zonisamide
    • Carbamazepine
    • Levetiracetam
    • Pregabalin
  • Oxytocin
  • Baclofen
  • Nalmefene – Opioid Antagonist Approved for Risk Reduction in Europe

SUMMARY REGARDING LONG-TERM TREATMENT FOR ALCOHOL DEPENDENCE

• Initiation of treatment for alcohol dependence prior to discharge may increase abstinence rates and engagement in ongoing outpatient treatment.
• Compliance rates at discharge do not differ from compliance to medications for other chronic disease states.
• Preferred agents are oral naltrexone, injectable naltrexone, or acamprosate; Disulfiram in specific patient populations.
• Combination therapy has not been studied.
• Treatment of co-morbid psychiatric illness is imperative.

UNDERSTANDING TREATMENT OF OPIOID WITHDRAWAL

• Opioid withdrawal syndrome occurs in almost 100% of individuals taking opioid medications for more than 2 weeks though severity varies greatly.
• Opioid withdrawal syndrome does not have an associated mortality but without treatment, the large majority of patients will relapse to opioids, which is associated with a very high mortality.
• Goal of hospital treatment for opioid withdrawal is to assess for complications of opioid use, to treat opioid withdrawal symptoms and prevent immediate relapse, and to refer the patient for ongoing treatment.
EVIDENCE-BASED TREATMENT OF OPIOID WITHDRAWAL

• Symptom-Triggered Opioid Withdrawal Protocol Using buprenorphine/naloxone and clonidine.

  • Clinical Opioid Withdrawal Scale (COWS) is a validated tool to monitor opioid withdrawal symptoms.1
  • Studies have demonstrated the efficacy of alpha-2 agonists (clonidine and lofexidine) for management of opioid withdrawal in multiple clinical settings.
  • Clonidine is widely used as an "off-label" treatment option for opioid withdrawal syndrome with good evidence to back it up.2,3
  • Lofexidine is currently being studied for use as an agent for opioid withdrawal management; a recent phase 3 study was terminated early due to significant outcomes favoring treatment with lofexidine.4


EVIDENCE-BASED TREATMENT OF OPIOID WITHDRAWAL

• Symptom-Triggered Opioid Withdrawal Protocol Using buprenorphine/naloxone and clonidine.

  • Buprenorphine has also been shown to facilitate withdrawal from opioids (particularly heroin) with multiple different treatment protocols.
    • 24-hour, high-dose buprenorphine treatment for detoxification from heroin effective1,2
    • One-day and three-day protocols using buprenorphine/naloxone sublingual tablets equally effective for rapid detoxification from heroin.1
    • Buprenorphine has been compared to clonidine in at least one study and demonstrated greater "treatment success", as measured by treatment retention.3
      • Study design not optimal to measure long-term outcomes.
      • Study design was not blinded.
    • Randomization did not distribute patients equally but favored the buprenorphine group 2:1

Imagine that the body's opioid balance is maintained like body temperature.

Each individual has a specific "opioid temperature" at homeostasis.

Introduction of external opioids to treat pain disrupts the opioid balance by artificially "raising the temperature."

Unfortunately, once the balance is disrupted enough, it can never really be restored.

The brain's chemical "set point," so to speak, has been permanently changed.

Addiction is therefore a chronic disease of the brain's neurochemical balance.
**TREATMENT OF OPIOID ADDICTION**

- Pharmacological Treatment Aims to Restore the Brain’s Neurochemical Balance by Using Medications.
  - Agonist Therapy (Opioid Maintenance Therapy)
  - Antagonist Therapy (Opioid Blocking Therapy)
- Behavioral Treatment Aims to Restore the Brain’s Neurochemical Balance by Using Techniques that Alter Thought Processes (which are in essence neurochemical processes).
- Self-Help Groups (12-Step Program) Facilitates Transcendence up Maslov’s Hierarchy of Needs.

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**PHARMACOLOGY FOR MAINTENANCE OF SOBRIETY FROM OPIOIDS — AGONIST THERAPY**

- **Buprenorphine**
  - Prescribed by a Physician Who has Undergone Additional Training and Received a Special DEA license (the “X-Number”).
  - Partial Agonist at the Mu-Opioid Receptor Creates a “Ceiling Effect” With Respect to Effects of the Medication.
  - Very Long-Acting Drug.
  - Combined with Naloxone (SUBOXONE® Formulation) to Avoid Abuse Via Injection Route.
- **Methadone**
  - Full Agonist at the Mu-Opioid Receptor.
  - Very Long-Acting Drug.
PHARMACOLOGY FOR MAINTENANCE OF SOBRIETY FROM OPIOIDS – AGONIST THERAPY

• “But Doc, Aren’t You Just Replacing One Drug With Another?”

• Yes, BUT:
  • Methadone and Buprenorphine are VERY LONG-ACTING OPIOIDS.
    • Very Flat Time-Versus-Concentration Curves.
    • Steady State Concentrations are Very Stable When Dosed Consistently.
  • Methadone and Buprenorphine Have Been Shown to Restore Normal Brain Physiology with Long-Term Use.
    • Long Term Use Restores Neurochemical Balance at a New Set Point.
    • Unfortunately, Discontinuation Typically Results in Imbalance Once Again.
    • Analogous to the Use of Basal Insulin in a Patient With Type 1 Diabetes Mellitus.

PHARMACOLOGY FOR MAINTENANCE OF SOBRIETY FROM OPIOIDS – AGONIST THERAPY

• Inpatient initiation of buprenorphine maintenance versus detoxification1:
  • Initiation of buprenorphine maintenance prior to discharge increased engagement in ongoing outpatient treatment for opioid use versus detoxification.
  • Patients initiated on buprenorphine maintenance prior to discharge also remained in treatment longer than patients who were detoxified.
  • These differences were statistically significant:
    • Buprenorphine Initiation Group: 8.5 Weeks
    • Detoxification Group: 0.4 Weeks

**PHARMACOLOGY FOR MAINTENANCE OF SOBRIETY FROM OPIOIDS – AGONIST THERAPY**

- Antagonist Therapy
  - Injectable Naltrexone (VIVITROL®)
    - Works by blocking (antagonizing) the opioid receptors
    - Intramuscular injection only approved for gluteal muscle administration
    - Requires dosing every 4 weeks (approximately every 28 days)
    - Non-addictive, unscheduled medication without DEA restrictions on use (i.e., any licensed provider can prescribe and administer)
- Theoretically "resets" the opioid receptor system
  - Cravings usually begin to fade within 1-2 weeks and remain dormant while the patient continues to use injectable naltrexone
  - Blocks attempts to get high with heroin. BUT dangerous for impulsive individuals who "chase the high" as continued attempts to overcome the blockade by using higher doses can lead to overdose death.
  - Effective medicine for maintenance of sobriety from heroin and other opioids.

**QUESTIONS?**