Pharmacological Management Of Alcohol Use Disorders

George Kolodner, M.D.
Chief Clinical Officer, Kolmac Outpatient Recovery Centers
Clinical Professor of Psychiatry,
Georgetown and University of Maryland Schools of Medicine

Sunil Khushalani, M.D.
Medical Director, Adult Service Line, Sheppard Pratt Health System
Clinical Assistant Professor of Psychiatry,
University of Maryland School of Medicine

OUTLINE

- Alcohol Basics
- Withdrawal Management
- Relapse Prevention

OUTLINE

ALCOHOL BASICS

KOLMAC

Sheppard Pratt

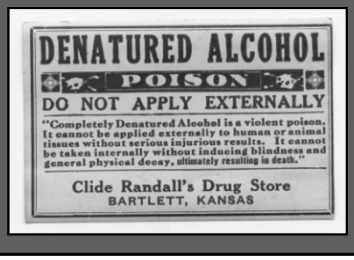
- Alcohol is the name for a group of substances
  - Beverage form: Ethanol/ Ethyl Alcohol

ALCOHOL BASICS

- Ethanol is made in two ways
  - Fermentation of sugar-containing fruits and grains
    - Beer (3-8% ethanol)
    - Wine (11-13% ethanol)
  - Distillation
    - Spirits (30+% ethanol)

ALCOHOL BASICS

- Denatured alcohol contains toxins to prevent consumption



ALCOHOL BASICS

- Standard Alcohol Drink
  (14 grams, 0.6 oz., 1.2 tablespoons)

ALCOHOL BASICS

- One standard drink raises blood level by 0.015 mg % to 0.20 mg % depending on weight and gender
  - 2 shots back to back → BAC = .03 -.04 mg%

ALCOHOL BASICS: Blood Alcohol Concentration

- Blood level decreases by approximately .02 mg% per hour
  - If initial level is .12 mg%, it would take 6 hours to get to zero
  - Allows extrapolation backward to determine level
    - If BAC = .12 mg % and last drink was 10 hours before, level when stopping drinking was .32 mg% (.12 + .20)
  - Diagnostic tool to determine high tolerance

ALCOHOL BASICS: Blood Alcohol Concentration

- Normal Tolerance
  - 0.10 mg%: legal intoxication
    0.40 mg%: lethal level
- Increased Tolerance
  (I can drink everyone else under the table)
  - No evidence of intoxication with BAC of .20
    Ambulatory- Blood with BAC of .40

ALCOHOL BASICS: Genetic Differences

- A disturbance of the balance between the reflective and impulsive parts of the brain which:
  - Begins with a genetic difference in sensitivities to certain substances common in our culture
  - Combines with environmental circumstances

ALCOHOL USE DISORDER: NEUROBIOLOGY

- The heavy alcohol use causes
  - A crippled prefrontal cortex
  - A dysregulated reward system
  - A disordered stress system
- A disruption in the balance between cortex and limbic system, which perpetuates pathological use

ALCOHOL USE DISORDER: NEUROBIOLOGY

- Toxic effects on organs

ALCOHOL BASICS:EFFECTS OF CHRONIC EXPOSURE

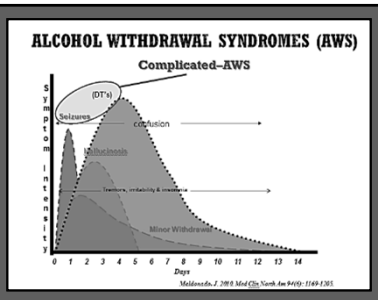
- Compensation of CNS neurotransmitter systems
  - Downregulation of GABA inhibition
  - Upregulation of glutamatergic and nor-adrenergic excitation

ALCOHOL BASICS:EFFECTS OF CHRONIC EXPOSURE

WITHDRAWAL MANAGEMENT

KOLMAC

Sheppard Pratt



ALCOHOL WITHDRAWAL

- American Society of Addiction Medicine (ASAM) Criteria
  - Levels
    - Outpatient: 2 (with or without onsite monitoring)
    - Inpatient: 4 (degree of medical availability)
  - Severity
    - Risk ratings: 4 (mild, moderate, significant, severe)

ALCOHOL WITHDRAWAL : Treatment Setting

- Overlap of outpatient and inpatient for moderate and severe withdrawal symptoms

ALCOHOL WITHDRAWAL : Treatment Setting

- Problem: How to predict withdrawal severity
  - Variability between patients and with a given patient
  - Withdrawal syndrome evolves rapidly
  - Preemptive treatment favored in order to stay ahead of symptoms
    - But unnecessary medicating is to be avoided

ALCOHOL WITHDRAWAL

- Alcohol disrupts multiple systems in the CNS
- Dose-related but individual variations reduce predictability

ALCOHOL WITHDRAWAL : Biological Complexity

- Syndrome evolves over time
- Delirium tremens is not responsive to medications that are effective for other withdrawal symptoms

ALCOHOL WITHDRAWAL : Biological Complexity

- 1800's to Present: Alcohol taper
- 1950's: Paraldehyde
- 1950's: Phenothiazines

ALCOHOL WITHDRAWAL : Abridged History

- 1960's: Benzodiazepines (current standard of care)
- 2000's: Anticonvulsants
- 2010's: Alpha-2 agonists

ALCOHOL WITHDRAWAL : Abridged History

- Benzodiazepines: Standard Fixed Intervals
- Benzodiazepines: Standard Symptom-triggered
- Anticonvulsants + Alpha-2 agonists (Alternative Non-benzodiazepine)
- Hybrid of standard and alternative

WITHDRAWAL MANAGEMENT: OPTIONS

- FIRST DAY: 50 mg hourly until anxiety is relieved (50 to 300 mg)
- FIRST NIGHT: 50 mg at bedtime

  Repeat hourly x 2 until asleep

SYMPTOM TRIGGERED WITHDRAWAL TAPER

- SECOND DAY: 50 mg x 1 – 2 in A.M.
- SECOND NIGHT: 50 mg at bedtime
  - Repeat in one hour if not asleep
- THIRD NIGHT: 50 mg at bedtime if needed

SYMPTOM TRIGGERED WITHDRAWAL TAPER

- Current standard of care is benzodiazepines

ALCOHOL WITHDRAWAL : A different approach

- Addictive potential
- Motor impairment, ataxia
- Sedation and cognitive changes interfere with psychosocial interventions

WHY AVOID BENZODIAZEPINES?

- Potential for delirium
- Limited effectiveness for delirium tremens
- Using GABA agent in a down-regulated system requires very large doses

WHY AVOID BENZODIAZEPINES?

- Act on hyperactive glutamatergic system
- Useful in mild to moderate severity
- Useful for extended use to reduce "post-acute withdrawal symptoms"

ALTERNATIVE AGENTS: ANTICONVULSANTS

- Problem: Not adequate alone for severe withdrawal (CIWA>20)

ALTERNATIVE AGENTS: ANTICONVULSANTS

- Avoid using benzodiazepines
- Use alpha-2 adrenergic agonists (clonidine, guanfacine (tenex) for 5 days
- Use anticonvulsant in combination
  - Gabapentin (Neurontin), carbamazepine (Tegretol), valproic acid (Depakote) for one week then reduce dose and continue for 6-12 months

ALCOHOL WITHDRAWAL : A NEW PROTOCOL

- New Thinking
  - Heavy use of alcohol has made the CNS insensitive to GABA agents ("down regulated")
  - Most alcohol withdrawal symptoms are due to adrenergic hyperactivity ("adrenergic storm")
  - Seizures are due to glutamatergic hyperactivity

ALCOHOL WITHDRAWAL : A different approach

- Anxiety
- Agitation
- Tremors
- Tachycardia
- Elevated Blood Pressure

S/S OF NORADRENERGIC HYPERACTIVITY

NEW APPROACH: CHOICE OF MEDICATIONS

- Gabapentin
  - Not metabolized by liver
    Some concern about addictive potential
    Alternatives: Carbamazepine, Valproic Acid
- Guanfacine
  - Less hypotension and sedation than clonidine

RETHINKING ALCOHOL WITHDRAWAL

- De-emphasizing distinction between acute and protracted withdrawal
  - Increase appreciation for how long it takes for the brain to heal- sleep problems and rebound hyperphagia can be seen for a year
  - Analogy to repeated brain trauma

RETHINKING ALCOHOL WITHDRAWAL

- Avoid cross-addiction to benzodiazepines
- Continue anticonvulsant such as neurontin (Gabapentin) for a year

RETHINKING ALCOHOL WITHDRAWAL

- Effect of Chronic Alcohol Heavy Intake
  - Down-regulation of GABA inhibition
  - Up-regulation of excitatory glutamatergic activity
  - **Up-regulation of norepinephrine activity ("adrenergic storm")**

WITHDRAWAL MANAGEMENT: TWO GOALS

- Short term: Safety and comfort
- Long term: Transition into ongoing treatment and recovery

ALCOHOL WITHDRAWAL : MILD OR MODERATE

- Day One
  - Guanfacine 1mg, gabapentin 300mg
  - Repeat in one hour if withdrawal discomfort > 2
  - Continue repeat of gabapentin as needed
  - Guanfacine 1 mg at bedtime
  - Librium 50mg QHS as needed

- First two weeks
  - Guanfacine 2 to 3 mg daily, reduce by 50% after first week, then discontinue
  - Gabapentin 1200 to 1800 mg daily
- In six months
  - Reduce and continue Gabapentin 600-1200 mg

ALCOHOL WITHDRAWAL : MILD OR MODERATE

- Day one is same except
  - Guanfacine 4 mg instead of 3 mg
  - Gabapentin 1500 to 2400 mg daily
  - Add Librium 50 mg prn during day up to 150 mg
    Bedtime: 50 mg, repeat as needed x 2

ALCOHOL WITHDRAWAL : SEVERE

- Day two
  - Librium 50-100 mg bedtime
- In six months
  - Reduce and continue Gabapentin 600-1200 mg

ALCOHOL WITHDRAWAL : SEVERE

ALCOHOL WITHDRAWAL : HYBRID PROTOCOL

- Day one
  - Symptom triggered benzodiazepine
  - Occasionally extend for day 2 for severe anxiety
- Day two and thereafter
  - Use anticonvulsant
- Add alpha-2 adrenergic agonist if history or presence of hallucinations

ALCOHOL WITHDRAWAL : TRACKING PROGESS

- CIWA-Ar (Clinical Institute Withdrawal Assessment for Alcohol–Revised)
  - Most commonly used
  - Many alternatives (Rastegar)
- Over-reliance on vital signs, especially BP

ALCOHOL WITHDRAWAL : TRACKING PROGRESS

- Using Withdrawal Discomfort Likert Scale to Guide Medication Decisions
  - If zero is feeling completely comfortable and ten is the worst withdrawal you have ever had, what number would you put on your withdrawal discomfort right now?
  - Goal is zero to one

- Dexmedetomidine (Precedex)
  - Parenteral alpha-2 agonist
  - Initially used for delirium, now applied to delirium tremens to reduce benzodiazepine use
    (Not FDA approved for delirium tremens)

ALCOHOL WITHDRAWAL : DELIRIUM TREMENS

- Decide: simultaneous versus deferring benzodiazepines
  - Assess whether underlying anxiety disorder requires treatment
  - Assess whether trauma disorder would be destabilized

ALCOHOL AND BENZODIAZEPINES

- Decide whether to use benzodiazepine or phenobarbital
- For withdrawal from benzodiazepines, extend taper over 4 to 8 weeks
  - More extended taper may be appropriate

ALCOHOL AND BENZODIAZEPINES

- Buprenorphine has a "ceiling effect" that prevents severe respiratory depression
  - Ceiling is gradually lifted by benzodiazepines
- Using benzodiazepines together with buprenorphine is not contraindicated but should be done with caution

ALCOHOL AND OPIOIDS

RELAPSE PREVENTION

KOLMAC

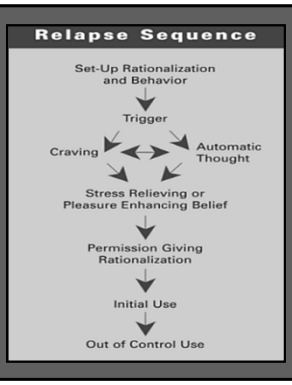
Sheppard Pratt

- Disulfiram (Antabuse)
- Naltrexone (Revia, Vivitrol)
- Acamprosate (Campral)

MEDICATIONS FOR RELAPSE PREVENTION

- Topiramate (Topamax)
- Clonidine (Catapres), Guanfacine (Tenex)
- Neither are FDA-Approved for this indication

MEDICATIONS FOR RELAPSE PREVENTION



- Exposure to the substance
  - Dopamine and Endorphin
  - Prefrontal cortex, Nucleus accumbens, Ventral pallidum

RELAPSE TRIGGERS: NEUROBIOLOGY

- Drug associated cues ("People, places, and things")
  - Dopamine, glutamate, and endorphin
  - Prefrontal cortex, amygdala, anterior cingulate gyrus

RELAPSE TRIGGERS: NEUROBIOLOGY

- Stress
  - Norepinephrine, Corticotropin-releasing factor (CRF)
  - Locus coeruleus, Bed nucleus of the stria terminalis

RELAPSE TRIGGERS: NEUROBIOLOGY

- Withdrawal from opioids and alcohol is associated with excessive norepinephrine activity in the brain stem (locus coeruleus)
  - Cause acute anxiety and agitation
  - Cause longer lasting sensitivity of stress regulating system

REDUCING STRESS-INDUCED RELAPSES

- Alpha-2 adrenergic agonists moderate the excessive NE activity and relieve withdrawal
  - Clonidine, guanfacine (Tenex)
- New: longer term use of alpha-2 agonists to disconnect stress pathway to reduce relapse

REDUCING STRESS-INDUCED RELAPSES

- Goal is for it to act as a deterrent
  - Removes expectation of pleasurable response to alcohol
  - Intends to prevent impulsive drinking or sampling of alcohol
- Allows the patient time to think of other ways to cope with acute cravings or stressful moments

DISULFIRAM

- The Disulfiram-Ethanol Reaction (DER)
  - Due to high levels of circulating acetaldehyde
- Is proportional to the dosage of both alcohol and disulfiram
- The risk of DER can last for up to 2 weeks after the last ingestion of alcohol

DISULFIRAM

- The Disulfiram-Ethanol Reaction (DER)
  - Symptoms can include flushing, nausea, tachycardia, dyspnea, hypotension, vomiting, cardiovascular collapse

DISULFIRAM

- Warn not only against drinking alcohol, but also alcohol in other hidden forms, such as cough syrups, mouth washes, alcohol in foods

DISULFIRAM

- Effective in early recovery only if administration is supervised

Superior to outcomes of other medications

Alcohol & Alcoholism Vol. 43, No. 1, pp. 53–61, 2008 doi:10.1093/alcalc/agm136
Advance Access publication 27 October 2007

A RANDOMIZED, MULTICENTRE, OPEN-LABEL, COMPARATIVE TRIAL OF DISULFIRAM, NALTREXONE AND ACAMPROSATE IN THE TREATMENT OF ALCOHOL DEPENDENCE

E. LAAKSONEN[1], A. KOSKI-JÄNNES,[4] M. SALASPURO,[2,3] H. AHTINEN,[5] and HANNU ALHO[2,3]*

of Alcohol Dependence Data (SADD), and quality of life (QL) measures. **Results:** All three study groups showed marked reduction in drinking, from baseline to the end of the study. During the continuous medication phase, treatment with DIS was more effective in reducing HDDs and average weekly alcohol consumption, and increasing time to the first drink, as well as the number of abstinent days. During the TM period, there were no significant differences between the groups in time to first HDD and days to first drinking.

DISULFIRAM

- Daily dose: standard is 250 mg
  - Absorption and sensitivity to reaction vary
  - Dr. Kolodner uses 125 mg (half tab) to reduce side effects and eliminate reaction to inadvertent alcohol contact
- Side effects
  - Liver function testing after 4 weeks to detect ALT>AST

DISULFIRAM

- It is also an inhibitor of Dopamine-β-hydroxylase (DBH)

DBH

Dopamine ⇒ Norepinephrine

Mechanism for usefulness with cocaine addiction

DISULFIRAM

- Beta endorphin is a neuromodulator which acts as a "pleasure chemical"
- Alcohol stimulates the release of β-endorphin
  - Alcohol activates reward centers in nucleus accumbens

ALCOHOL BASICS-ALCOHOL AND β-ENDORPHIN

- Alcoholics with strong positive family history and onset before 25 have:
  - Low baseline β-endorphin levels
  - High β-endorphin spikes
  - Increased sensitivity of μ-receptors
    A118G allele codes for mu receptor sensitivity
  - Result: **more intense** euphoric response to alcohol

ALCOHOL BASICS-ALCOHOL AND β-ENDORPHIN

- Naltrexone reduces euphoric response to alcohol by blocking μ-opioid receptor
- Naltrexone reduces alcohol craving by unknown mechanism.
- "Revia": oral, 50mg q24 hours
- "Vivitrol": gluteal 380 mg IM injection, q4 weeks

NALTREXONE

- Data from 50 RCTs and nearly 8000 participants done in 2010
  - Compared to placebo, naltrexone significantly reduced heavy drinking by about 17% and reduced drinking days by about 4%. It also produced reductions in levels of GGT

NALTREXONE

- Developed with the aim of improving treatment adherence in patients treated with naltrexone for alcohol dependence
  - Extended-release intramuscular naltrexone recipients had greater reductions in the number of drinking days (by 25%) compared with placebo recipients

NALTREXONE:VIVITROL

- Glutamate is the primary CNS excitatory neurotransmitter
- Alcohol antagonizes glutamate
- Cessation of drinking leaves the alcoholic in a state of hyper-glutamatergic excitation
  - Contributes to post acute withdrawal symptoms and relapse

ALCOHOL BASICS-ALCOHOL AND GLUTAMATE

- Acamprosate is modified taurine, an inhibitory neurotransmitter
- Acamprosate reduces glutamate hyperactivity over time
- It can have a settling effect on patients with alcohol use disorder
  - Power of relapse triggers is reduced

ACAMPROSATE

- Superior to placebo in 13 of 17 European studies
  - Poorer outcomes in U.S. studies and usage

ACAMPROSATE

- Constellation of difficult to measure symptoms including sleep, mood, irritability, cognitive that persist for months and contribute to relapse
  - Ameliorated by gabapentin and acamprosate

POST-ACUTE ALCOHOL WITHDRAWAL

ARE MEDS UNDERUTILIZED?

- In the fiscal year 2012, there were 444,000 veterans with a documented diagnosis of alcohol use disorder- only 5.8% received pharmacotherapy
- In a survey of practices among North Carolina mental health providers only 3% of sufferers receive FDA-approved treatment.

ARE MEDS UNDERUTILIZED?

- Perception that medications have little effect on recovery
- A lack of appreciation that even small to medium effect on outcomes provides an important improvement in relapse rates

SOME REASONS

- A reluctance to prescribe medications for a condition that is thought to be treatable through other techniques, such as motivational therapy or AA
- Failure to see the biological side of addiction

SOME REASONS

- Lack of support or opposition from the recovery community
- Financial barriers

SOME REASONS