ALCOHOL

Ricardo Restrepo, MD, MPH
Associate Clinical Professor of Psychiatry, University of California, Irvine
Substance Abuse Treatment Program-SATP
Buprenorphine Clinic Medical Director
VA Long Beach Healthcare System
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Disclosure Information

Ricardo Restrepo, MD, MPH

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OUTLINE

1. Historical view
2. Neurobiology
3. Epidemiology
4. SBIRT and Clinical Screening Test
5. Diagnosis
6. Biomarkers
7. Phases of Alcohol Treatment and Related Syndromes
8. CIWA-Ar and Management
9. Relapse Prevention Pharmacotherapy and Psychotherapy
10. New Directions
11. Conclusions
After the flood, Noah plants a vineyard, makes wine and gets drunk. (Genesis 9:21)

"Who hath woe? Who hath sorrow? Who is always fighting?
Who is always complaining? Who hath wounds without cause?
Who has bloodshot eyes?

They who tarry long at the wine; when it sparkles in the cup.

Don't let the smooth taste deceive you. For in the end it bites like a poisonous serpent. And you will say, 'They hit me, but I didn't feel it.'

Your eyes will see strange visions and you will say strange thoughts. Yet when you awaken, you seek it yet again.”

(Proverbs 23:29 (-1,000 BC)
Pliny the Elder: Gaius Plinius Secundus

Naturalis Historia: “drunkeness brings pallor and sagging cheeks, sore eyes, and trembling hands that spill a full cup, of which the immediate punishment is a haunted sleep and unrestful nights…”
National Prohibition took effect in 1920. These are some of the laws before Prohibition and also the 18th amendment and Volstead Act.

1697 The first American alcohol law was put into effect in New York. The law said that all saloons must close on Sundays because Sunday is a day for worship not drinking.

1735 The first statewide prohibition began in the state of Georgia.

1851 Maine was the 2nd state in the history of America to attempt a statewide prohibition, and it turned out to be a major success. By 1855, 12 other states had joined Maine in becoming dry. These were the first successful alcohol Prohibition laws passed in the United States.

1880 After the Civil War, women joined the dries and soon the temperance movement was back in full force. The WCTU was formed and the Prohibition Party became more powerful. All sorts of Prohibitions, including alcohol, tobacco, and closing all theaters were proposed, but the only one that ever caught on was the alcohol Prohibition.
By 1900 More than half of the States had become dry. Because the postal service was run by the federal government instead of the state government, liquor could be mail ordered from a wet state.

1913 The Interstate Liquor Act was passed. This act made it illegal to send liquor to a dry state

January 1919 The 18th Amendment was ratified and all hard liquor with over 40% alcohol content (drinks over 80 proof) were banned. Officially, it banned the “manufacture, sale, or transportation of intoxicating liquors…for beverage purposes.” The Amendment took effect one year later on January 29, 1920.

October of 1919 The Volstead Act was passed. The Volstead Act banned all alcohol that had more than 1/2% alcohol content. This effectively banned all forms of alcoholic beverages, with the exception of some non-alcoholic beers.
Alcohol Abuse/Dependence a disease?
<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>GABA</td>
<td>CNS Inhibition</td>
</tr>
<tr>
<td>Glutamate</td>
<td>CNS Excitation</td>
</tr>
<tr>
<td>Opioid</td>
<td>Euphoria</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Addiction</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Impulsivity</td>
</tr>
<tr>
<td>Cannabinoid</td>
<td>Pleasant Feeling</td>
</tr>
</tbody>
</table>
Steps in Synaptic Transmission

PRESYNAPTIC TERMINAL

Ca\textsuperscript{2+} channel

Neurotransmitter uptake

POSTSYNAPTIC DENDRITE

Ligand-Gated Ion Channels

POSTSYNAPTIC POTENTIAL

Neurotransmitter uptake

+++

+++

Ca\textsuperscript{2+} channel
Acute Alcohol Intake

GLUTAMATE +

GABA -
Chronic Alcohol Intake

GLUTAMATE +

GABA -
Prevalence of Alcohol Abuse/Dependence

- Estimated 14-18 million alcohol-abusing or alcohol-dependent individuals
  - Approximately half are alcohol dependent
- Prevalence similar to other chronic diseases such as asthma, diabetes, and depression
- Economic loss of $223.5 billion in societal costs
- 79,000 deaths annually
- Causes many other health problems either directly or indirectly

Grant BF, et al. Arch Gen Psychiatry. 2004;61:807-816; NIAAA National Institute on Alcohol Abuse and Alcoholism (1994, 2000a, 2000b); Centers for Disease Control and Prevention (1999); National Center for Health Statistics; McLellan et al. (2000); American Lung Association, American Heart Association and National Pharmaceutical Council
## Abuse/Dependence

### ABUSE

- 1 or more
  - Role failure
  - Risk of harm
  - Run-ins with law
  - Relationship trouble

### DEPENDENCE

- 3 or more
  - Tolerance
  - Withdrawal
  - Unable to limit
  - Unable to cut down
  - ↑ Time with alcohol
  - ↓ Time elsewhere
  - Use despite problems

**In same 12 months**
DSM-V Proposed Changes
Criteria for Alcohol Use Disorders

1. USE IN LARGER AMOUNTS / LONGER PERIODS THAN INTENDED
2. UNSUCCESSFUL EFFORTS TO CUT DOWN
3. EXCESSIVE TIME SPENT TAKING DRUG
4. FAILURE TO FULFILL MAJOR OBLIGATIONS
5. CONTINUED USE DESPITE KNOWLEDGE OF PROBLEMS
6. IMPORTANT ACTIVITIES GIVEN UP
7. RECURRENT USE IN PHYSICALLY HAZARDOUS SITUATIONS
8. CONTINUED USE DESPITE SOCIAL OR INTERPERSONAL PROBLEMS
9. TOLERANCE
10. WITHDRAWAL
11. CRAVING

SEVERITY:
0 TO 1 CRITERIA: NO DIAGNOSIS
2 TO 3 CRITERIA: MILD
4 TO 5 CRITERIA: MODERATE
6 OR MORE CRITERIA: SEVERE
Underdiagnosis and Unmet Treatment Needs

- Physicians are often not comfortable assessing for Alcohol Use Disorders

- National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) data indicate that only about 20% of adults with alcohol abuse or dependence have ever received treatment:
  - Self-help groups
  - Psychotherapy
  - Pharmacological treatments
How much is “too much”? 

- **MEN:**
  - 5 or more standard drinks in a sitting.
  - (15 or more per week.)

- **WOMEN:**
  - 4 or more standard drinks in a sitting.
  - (8 or more per week.)
What is a Standard Drink?

- **1 Standard Drink = 14 gr. (0.6 oz.) of pure alcohol.**
- **The average person metabolizes about 1 Standard Drink per hour.**

### Quantities

- **12 oz**
  - beer or cooler

- **8-9 oz**
  - malt liquor
  - 8.5 oz shown in a 12-oz glass that, if full, would hold about 1.5 standard drinks of malt liquor

- **5 oz**
  - table wine

- **3-4 oz**
  - fortified wine
  - (such as sherry or port)
  - 3.5 oz shown

- **2-3 oz**
  - cordial, liqueur, or aperitif
  - 2.5 oz shown

- **1.5 oz**
  - brandy
  - (a single jigger)

- **1.5 oz**
  - spirits
  - A single jigger of 80-proof drink (gin, vodka, whiskey, etc.) undiluted, and in a highball glass with ice to show level before adding mixer

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Adapted from www.niaaa.nih.gov.
The Rule of Twenties

- **MEN:**
  - Each drink adds 20 mg/dL to one’s BAL.

- **WOMEN:**
  - Each drink adds 40 mg/dL to one’s BAL.

We metabolize 20 mg/dL every 60-90 minutes (zero order kinetics).
Women and Pregnancy

- Volume of distribution = Total Body Water

  Woman

- Fetal Alcohol Spectrum disorders (FASD): Growth retardation, Facial malformations, Small head, Greatly reduce intelligence

- 40,000 infants per year in US

SAMHSA Fetal Alcohol Spectrum Disorders. Center For Excellence. Accessed Sept, 1 2012
Screening quickly assesses the severity of substance use and identifies the appropriate level of treatment.

Brief intervention focuses on increasing insight and awareness regarding substance use and motivation toward behavioral change.

Referral to Treatment provides those identified as needing more extensive treatment with access to specialty care.

www.niaaa.nih.gov/guide
http://www.sbirtcolorado.org/healthcare_videosandwebcasts.php
Screening tool

The CAGE Questionnaire

- Cut Down
- Annoyed
- Guilty
- Eye-Opener

2 or more positive responses are strongly associated with alcohol dependence

National Institute on Alcohol Abuse and Alcoholism (NIAAA): “Helping Patients Who Drink Too Much”
The Role of Biomarkers in The Treatment of ETOH

- Provide objective outcome measures in alcohol research or evaluating an alcohol treatment program
- Screen for individuals unable/unwilling to accurately report drinking behavior (e.g. fear, embarrassment, or adverse consequences)
- Evidence of abstinence in individuals prohibited from drinking
- Enhance patient motivation to stop/reduce drinking
- Diagnosis tool by assessing contribution of alcohol to the disease
- Identify relapse early
- Fear of detection by biomarkers may dissuade drinking
BAC

1 drink → BAC = ~15 mg% (0.015 g/dl)

<table>
<thead>
<tr>
<th>BAC mg%</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-99</td>
<td>Loss of muscular coordination</td>
</tr>
<tr>
<td>100-199</td>
<td>Neurologic impairment with prolonged reaction time, ataxia, incoordination, and metal impairment</td>
</tr>
<tr>
<td>200-299</td>
<td>Vey obvious intoxication, except in those with marked tolerance. Nausea, vomiting, marked ataxia</td>
</tr>
<tr>
<td>BAC mg%</td>
<td>Clinical Manifestations</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>300-399</td>
<td>Hypothermia, severe dysarthria, amnesia, Stage I anesthesia</td>
</tr>
<tr>
<td>400-799</td>
<td>Onset of alcoholic coma, with precise level depending on degree of tolerance, progressive obtundation, decreases in respiration, blood pressure, and body temperature, urinary incontinence or retention, reflexes markedly decreased or absent</td>
</tr>
<tr>
<td>600-899</td>
<td>Often fatal because of loss of airway protective reflexes from airway obstruction by flaccid tongue, from pulmonary aspiration of gastric contents, or from respiratory arrest from profound central nervous system obstruction</td>
</tr>
</tbody>
</table>
Types of ETOH Biomarkers

**INDIRECT TESTS**

- Manifestations of **organ damage** often due to drinking
  - gamma glutamyltransferase (GGT)
  - aspartate amino transferase (AST, SGOT)
  - alanine amino transferase (ALT, SGPT)
  - macrocytic volume (MCV)

- Reflections of alcohol’s effects on other **metabolic processes**
  - carbohydrate-deficient transferrin (CDT)

**DIRECT TESTS**

- Reflections of alcohol use
  - ethyl glucuronide (EtG) and ethyl Sulfate (EtS)
  - Phosphatidylethanol
Window of Assessment for Various Alcohol Biomarkers

SAMHSA (Substance Abuse and Mental Health Services Administration) The Role of Biomarkers in the treatment of alcohol use disorders, 2012 Revision
### Characteristics of Assessment for Various Alcohol Biomarkers

<table>
<thead>
<tr>
<th>Marker</th>
<th>Time to Return to Normal with Abstinence</th>
<th>Level of Drinking</th>
<th>Comments</th>
<th>Blood test normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>GGT</td>
<td>2-4 weeks of abstinence</td>
<td>~ 5 drinks (120 g/day) for several weeks</td>
<td>Many sources of false positives—liver disease, smoking, obesity, age, anticonvulsants, etc.</td>
<td>W: 0-45 U/L M: 0-53 U/L</td>
</tr>
<tr>
<td>SGOT/AST</td>
<td>2-4 weeks of abstinence</td>
<td>Unknown but heavy</td>
<td>Many sources of false positives (see GGT)</td>
<td>10 - 34 U/L</td>
</tr>
<tr>
<td>SGPT/ALT</td>
<td>2-4 weeks of abstinence</td>
<td>Unknown but heavy</td>
<td>Many sources of false positives (see GGT) Less sensitive than AST</td>
<td>8-37 U/L</td>
</tr>
<tr>
<td>MCV</td>
<td>Up to several months</td>
<td>Unknown but heavy</td>
<td>Slow return to normal limits even with abstinence renders it a poor independent indicator of relapse. More specific than GGT. Unlike other markers, no strong gender effect</td>
<td>80-100fL</td>
</tr>
<tr>
<td>CDT</td>
<td>2-3 weeks</td>
<td>&gt;60g/day for 2 weeks</td>
<td>Few sources of false positives. Good marker of relapse</td>
<td>&lt;60 mg/L</td>
</tr>
</tbody>
</table>
## Diagnostic Sensitivity and Specificity of Biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDT</td>
<td>69</td>
<td>92</td>
</tr>
<tr>
<td>CDT/transferrin</td>
<td>65</td>
<td>93</td>
</tr>
<tr>
<td>GGT</td>
<td>73</td>
<td>75</td>
</tr>
<tr>
<td>AST</td>
<td>50</td>
<td>82</td>
</tr>
<tr>
<td>ALT</td>
<td>35</td>
<td>86</td>
</tr>
<tr>
<td>MCV</td>
<td>52</td>
<td>85</td>
</tr>
</tbody>
</table>

Phases of Alcoholism Treatment

- **Detoxification:**
  - Primary goal is to achieve an alcohol-free state
  - Wide spectrum of severity
  - Drug-specific syndromes: opiates, cocaine, alcohol, benzodiazepines

- **Relapse prevention:**
  - Primary goal is to maintain an alcohol-free state
  - Chronic treatment
Introduction Alcohol Withdrawal

- Epidemiology
- Neurobiology
  - Neurotoxicity
  - Kindling
- Management of Alcohol Withdrawal
  - Benzodiazepines
  - Anticonvulsants
- Real World Implications
  - Outpatient vs. Inpatient
  - Evaluation and Management
Epidemiology of Alcohol Withdrawal

- Not well studied
- Significant symptoms occur in 13% to 71% of individuals presenting for detoxification
- Up to 10% of individuals undergoing alcohol withdrawal require inpatient medical treatment
- Estimated mortality up to 2%

Alcohol Withdrawal and Kindling

- Repeated episodes of alcohol withdrawal likely to worsen
- Exacerbation of symptoms may be due to a kindling process
- Positive relationship of alcohol withdrawal seizures to repeated detoxification
Managing Alcohol Withdrawal

- Principles of treatment
  - Alleviate symptoms
  - Prevent progression of symptoms
  - Treat underlying comorbidities
Alcohol Withdrawal Treatment

- Substitute cross-dependent drug (benzodiazepine)
- Gradually withdraw substitute drug
- Supplement vitamins and minerals
  - Thiamine
  - Folic acid
  - Multivitamin
- Supportive treatment
  - Decrease stimulation, increase fluid and caloric intake
Alcohol Withdrawal Treatment
Thiamine Deficiency

agogue

Thiamine
- Important cofactor for several enzymatic reactions
  - Cerebral glucose utilization
  - Glutamate elimination

Wernicke’s Encephalopathy
- Partial to complete paralysis of extra ocular muscles
- Nystagmus
- Ataxia
- Mental disturbances
- Mortality: 10-20% if untreated
- Treatment: Thiamine replacement PRIOR dextrose administration

Korsakoff’s Psychosis
- Antegrade amnesia
- Confabulations
States of AWS

1. Autonomic Hyperactivity
2. Hallucinations
3. Neuronal excitation
4. Delirium Tremens

There is not necessarily a linear progression
 STATES OF AWS

- **Autonomic Hyperactivity**
  - Clear Sensorium
  - Tremulous
  - Diaphoresis
  - Anxiety
  - Nausea/Vomiting
  - Increase cathecolamines in urine, serum and CSF
  - Start 6 hrs after last drink
  - Peak 24-48 hrs

- **Hallucinations**
  - Most common = VISUAL

- **Neuronal excitation**
  - Seizures (Generalized Tonic–Clonic)
  - Up to 10%
  - Most common in first 12-48 hours after last drink
DELIRIUM TREMENS (DTs)
- Most often occur within 72 hours after the last drink
- Delirium with Tremor
- Autonomic hyperactivity
- Hallucinations
- Electrolyte abnormalities
- Dehydration
- Hemodynamic instability
- Mortality up to 15%
  - Cardiovascular/respiratory collapse
CIWA-Ar
(Clinical Institute Withdrawal Assessment of Alcohol, Revised)

- It requires **under two minutes** to administer
- It requires no medial knowledge
- It provides you with a quantitative score that predicts the severity of withdrawal from alcohol
Assessment of Alcohol Withdrawal
CIWA-Ar

1. **Nausea/Vomiting: 0-7**
   - 0 – none
   - 7 – constant nausea and frequently dry heaves and vomiting

2. **Tremors: 0-7**
   - Have patient extend arms & spread fingers
   - 0 – none
   - 7 – severe, even with arms not extended

3. **Anxiety: 0-7**
   - 0 – no anxiety, patient at ease
   - 7 - equivalent to acute panic states seen in severe delirium or acute schizophrenic reactions

4. **Agitation**
   - 0 – normal activity
   - 7 – paces back and forth, or thrashes about
5. **Paroxysmal Sweats: 0-7**
   - 0 – no sweats
   - 7 - drenching sweats

6. **Orientation and Clouding of Sensorium: 0-4**
   - Ask, “What day is this? Where are you? Who am I?”
     - 0 - Oriented
     - 4 - Disoriented to place and/or person

7. **Tactile Disturbance: 0-7**
   - Ask, “Have you experienced any itching, pins & needles sensation, burning or numbness, or a feeling of bugs crawling on or under your skin?”
     - 0 – none
     - 7 – continuous hallucination
8. **Auditory Disturbances: 0-7**
   - Ask, “Are you more aware of sounds around you? Are they harsh? Do they startle you? Do you hear anything that disturbs you or that you know isn’t there?”

9. **Visual Disturbances: 0-7**
   - Ask, “Does the light appear to be too bright? Is its color different than normal? Does it hurt your eyes? Are you seeing anything that disturbs you or that you know isn’t there?”

10. **Headache: 0-7**
    - Ask, “Does your head feel different than usual? Does it feel like there is a band around your head?” Do not rate dizziness or lightheadedness.
CIWA-Ar Determining Need of Pharmacotherapy

- <8: Minimal – Mild AW, Drug therapy not necessarily indicated
- 8-14: Moderate AW, Drug therapy indicated.
- >15: Severe, Drug therapy absolutely indicated, consider inpatient treatment

http://www.chce.research.va.gov/apps/PAWS/quiz/q1.html
Mechanisms Underlying Alcohol Withdrawal

- Multiple neuroadaptive changes in CNS
  - Decreased GABA activity
  - Increased glutamate activity
  - Upregulated calcium channel activity
  - Increased noradrenergic activity

- Alcohol withdrawal is associated with increased CNS activity

CNS=central nervous system; GABA=gamma-aminobutyric acid.
Anton RF, Becker HC, eds. Pharmacotherapy and pathophysiology of alcohol withdrawal. (Handbook of Experimental Pharmacology.) 1995.
Effects of Alcohol on Neurotransmitter Balance

- **Normal**
  - Inhibition (GABA)
  - Excitation (Glutamate)

- **Acute Alcohol Intake**
  - Alcohol
  - GABA
  - Glutamate

- **Chronic Intake/Dependence**
  - Alcohol
  - Adaptation
  - GABA
  - Glutamate

- **Acute Withdrawal**
  - Adaptation
  - GABA
  - Glutamate

- **Protracted Withdrawal**
  - Adaptation
  - GABA
  - Glutamate

Alcohol Detoxification
Use of Benzodiazepines

- First line agent
- Loss of inhibition/sedation due to lack of ETOH
- Treatment: Replace the GABA activation (inhibition)
- Benzodiazepines:
  - If hepatic impairment: oxazepam or lorazepam
  - Provide dosing for 24 hour intervals – patient must be re-evaluated before more is provided
    - Vital Signs
    - CIWA-Ar
Benzodiazepines options

- **Chlordiazepoxide**
  - Only available in oral form
  - Longer half life than most benzos

- **Diazepam**
  - Lipophilic → rapid onset of action

- **Lorazepam**
  - Simple metabolism of hepatic glucoronidation
  - Ideal for patients with cirrhosis/liver damage and elderly population
Indications for Outpatient withdrawal treatment

- CIWA <8 or some with CIWA 8 – 15
- No hx. of AW seizures/delirium
- No serious medical/surgical problems
- No serious psychiatric/drug hx
- Social support
- Supervision/housing available
Indications for Inpatient withdrawal treatment

- History of DTs or withdrawal seizures
- Alcohol withdrawal severity (CIWA>10) + other criteria
- Pregnancy
- Major medical/surgical problems
- Inability to tolerate oral medication
- Imminent risk to harm himself and/or others
- Active psychosis or cognitive impairment
- Recurrent unsuccessful attempts at ambulatory detoxification
TREATMENT OF MILD-MODERATE ALCOHOL WITHDRAWAL
CIWA-Ar- 8 to 20

LONG-ACTING BENZODIAZEPINES:
- CHLORDIAZEPOXIDE (Librium) 50-100 mg po q 6-8 hrs.
- DIAZEPAM (Valium) 10-20 mg po q 6-8 hrs.

SHORT-ACTING BENZODIAZEPINES:
- LORAZEPAM (Ativan) 2-4 mg po q 1-4 hrs.
TREATMENT OF SEVERE ALCOHOL WITHDRAWAL
CIWA-Ar >20

- DIAZEPAM 10 mg IV
  - REPEAT 5 mg IV q 5 min until calm

- LORAZEPAM 4 mg po q 1 hr, PRN
  - MODERATE TO SEVERE LIVER DISEASE
  - ELDERLY OR CONFUSED PATIENTS
  - VERY ILL OR DEBILITATED PATIENTS
  - CAN BE GIVEN PO, IV OR IM
Alcohol Detoxification
Use of Anticonvulsants

ANTICONVULSANTS REDUCE GABA ACTIVITY

- CBZ: Reduced rebound withdrawal & post-detox drinking (Malcolm, 2002)

- Gabapentin normalizes alcohol-induced effects on GABA and glutamate; has no hepatic metabolism

- Gabapentin more effective than lorazepam in reducing post-detox drinking (Myrick, 2009)

- Gabapentin, divalproex & vigabatrin may prove useful
- Caution: CBZ & divalproex have limited use in patients with severe hepatic or hematologic disease
Alcohol Detoxification
Anticonvulsants effectiveness and limitations

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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</thead>
<tbody>
<tr>
<td>No abuse liability</td>
<td>Limited clinical experience</td>
</tr>
<tr>
<td>Cognition</td>
<td>Hematological side effects</td>
</tr>
<tr>
<td>Neuroprotective</td>
<td>Liver toxicity</td>
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<tr>
<td>Protracted Withdrawal</td>
<td></td>
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</tbody>
</table>
When to consider Pharmacotherapy

- Anticraving Medication as the new standard of care
  - Consider, immediately post-detoxification for **ALL** alcoholics
  - Efficacy requires counseling and/or frequent physician monitoring

- Most FDA approved medications for SUDs can be used in outpatient settings
- Exception: Methadone maintenance therapy: can only be used for treatment of opioid addiction in licensed opioid treatment programs
Alcohol Dependence (Relapse Prevention) FDA Approved

- Naltrexone (oral and injectable)
- Disulfiram
- Acamprosate
Pharmacotherapy of Alcohol Dependence: Naltrexone-oral

Mechanism of Action

- Reduces positive reinforcement (reward craving)
  - Potent inhibitor at mu opioid receptors
- Modulates the mesolimbic dopamine system in the VTA & projections to the nucleus accumbens
- The patient does not experience the full euphorogenic/reinforcing effect of alcohol.
  - because suppresses/reduces endogenous opioids (beta-endorphin) involved in the reinforcing (pleasurable) effects of alcohol and possibly craving
- Prevents a slip from becoming a full-blown relapse
Pharmacotherapy of Alcohol Dependence: Naltrexone-oral Effectiveness

- Effective in reducing relapse to heavy drinking.

- A meta-analysis of 27 randomized controlled trials found a 36% reduction in the rate of relapse to heavy drinking.

- Medication compliance may be a limiting factor in oral treatment.

HEAVY DRINKING = 5 or more drinks/day for a man - 4 or more drinks/day for a woman.

Pharmacotherapy of Alcohol Dependence: Naltrexone-oral Dosing and Safety

- Oral Naltrexone Hydrochloride
  - FDA approved dose: 50 mg per day

  - Antagonizes opioid-containing agents, but no other significant drug-drug interactions.

  - Some have used 100 mg daily with rationale that naltrexone has been effective for heroin addiction at doses of 100mg-100mg-150 mg q Monday, Wednesday and Friday; so an effective plasma concentration can be obtained even if some doses are missed.
Pharmacotherapy of Alcohol Dependence: Naltrexone-oral
Dosing and Safety

- **Side effects**
  - GI: abdominal pain, decreased appetite, nausea
  - Sedation: daytime sleepiness, fatigue, insomnia, headache

- **Reversible hepatoxicity**
  - LFT’s should be monitored closely

- **Works best with complaint patients**
  - Requires counseling (CBT) or frequent MD monitoring visits (Project Combine, 2006)
  - Efficacy questioned in women (O’Malley, 2007)

**Naltrexone-Oral in the Treatment of Alcohol Dependence**

Volpicelli et al., Arch Gen Psychiatry, 1992
Pharmacotherapy of Alcohol Dependence: Long Acting Naltrexone (IM)

- Extended-Release Injectable Naltrexone
  - 1 injection per month/ 380 mg
  - 100 μm diameter microspheres of naltrexone and polymeric matrix.
  - Advantages: once a month injection can be done in clinician’s office
  - Better adherence with once monthly dosing
  - More stable plasma concentrations compared to the oral formulation

Pharmacotherapy of Alcohol Dependence:
Long Acting Naltrexone (IM)
Dosing and Safety

- Extended-Release Injectable Naltrexone

- Side effects: nausea & headaches; more sedation than with the oral formulation

- LFT’s should be monitored closely

- Injection site reactions possible

- Best results in patients sober 1 week prior to starting the medication

- Efficacy shown in more severe alcoholics

- Reduction in heavy-drinking days (48.9% vs 30.9% on placebo)

Naltrexone-injectable in the Treatment of Alcohol Dependence

Results: Heavy Drinking Days

Garbutt et al., 2005
Protracted Withdrawal Symptom

- Sleep dysregulation
- Irritability
- Mood instability
- Anxiety
Pharmacotherapy of Alcohol Dependence: Acamprosate
Mechanism of Action

- Stabilizes glutamatergic neurotransmission altered during withdrawal (Littleton 1995)

- Alters GABA & NMDA systems
  - Restores balance between inhibitory & excitatory neurotransmission

- Anticraving, reduced protracted withdrawal

- Reduce negative reinforcement (abstinence craving)

- No abuse liability, hypnotic, muscle relaxant, or anxiolytic properties
Pharmacotherapy of Alcohol Dependence: 
Acamprosate 
Effectiveness

- Effective in improving abstinence.

- The Kranzler and Gage (2008) re-analysis of the European data found that ~20% of patients treated with acamprosate were abstinent after a year of treatment (vs ~10% for placebo).

- The US trial showed efficacy only in patients motivated for abstinence.

Pharmacotherapy of Alcohol Dependence: Acamprosate
Dosing and Safety

666 mg three times a day

Excreted by the kidneys; no liver metabolism
Contraindicated: significant renal disease with creat cl <30ml/min

Mild diarrhea (16% acamprosate vs. 10% placebo)

Recommendation: patients with hepatic disease or those treated with opioids. Advantage when a patient is taking multiple medications

No drug-drug interactions.
Acamprosate in the Treatment of Alcohol Dependence

% of Patients Abstinent

Treatment Period*

Follow-Up Period†

- Acamprosate (N=136)
- Placebo (N=136)

*p=0.001; †p=0.003

Sass et al., Arch Gen Psychiatry, 1996
Pharmacotherapy of Alcohol Dependence: Disulfiram Mechanism of Action

Ethanol: $\text{CH}_3\text{CH}_2\text{OH}$

Acetaldehyde: $\text{CH}_3\text{COH}$

Acetate: $\text{CH}_3\text{COOH}$

- Alcohol dehydrogenase (ADH)
- Acetaldehyde dehydrogenase (ALDH)
- P450 2E1 (microsomes)
- Catalase (peroxisomes)
Pharmacotherapy of Alcohol Dependence: Disulfiram
Mechanism of Action

- Alcohol $\rightarrow$ Acetaldehyde $\rightarrow$ Acetate
- Disulfiram irreversibly binds to acetaldehyde dehydrogenase inhibiting the metabolism of acetaldehyde to acetate.
- Acetaldehyde accumulates resulting in a violent reaction (nausea, vomiting, flushing).
Double-blind, placebo-control study design is not helpful as both the medication and the placebo pills may (or may not) result in fear of drinking.

Most studies are negative, but supervised disulfiram may be helpful.

Pharmacotherapy of Alcohol Dependence: Disulfiram
Dosing and Safety

- 250-500 mg daily.

- Some liver toxicity; monitor LFTs. Caution with CAD. Contraindicated: psychosis, significant liver disease, esophageal varices, pregnancy, impulsivity (Barth et al., 2010)

- Inhibits hepatic microsomal enzymes and increases drug levels (phenytoin, warfarin, isoniazid, metronidazole, TCA and benzodiazepines among others)

- SIDE EFFECTS: skin/acneiform eruptions, drowsiness, headache, metallic taste, decreased libido/potency

Disulfiram in the Treatment of Alcohol Dependence

Disulfiram and Abstinence Rates (VA Cooperative Study)

Noncompliant (80%)
Compliant (20%)

Disulfiram 250 mg (N=202 men)
Disulfiram 1 mg (N=204 men)
Placebo (N = 199 men)

Fuller RK et al. *JAMA*. 1986; 256:1449-1455
Naltrexone and acamprosate have different mechanisms of action and may work synergistically on cravings:

- Naltrexone on positive reinforcement
- Acamprosate on negative reinforcement

Medications and psychotherapy.
Abstinence rates during a 12-week trial with:

- Naltrexone 50 mg QD,
- Acamprosate 666 mg TID.

The combination of the two medications helped alcoholics stay abstinent ($P=0.002$) better than each drug alone.

Adapted from Kiefer F et al. Arch Gen Psychiatry. 2003;60:96.
Project MATCH

- Compared outcome efficacy for patients matched to treatments based on a priori hypotheses about 11 client attributes
- Treatment was for 12 weeks; follow-ups continued for years
- 12-Step programs, CBT and MET were compared
- Each of the three methods helped in the treatment of alcoholism
- There were a few matching effects, and they were weak
The COMBINE Study

- 1383 patients with alcohol dependence randomized to varying combinations of oral Naltrexone, Acamprosate, combined behavioral intervention (CBI) and medical management (MM)

- Patients received naltrexone, acamprosate, both, or neither

- Half of patients received psychotherapy in addition to medical management

- One patient cohort received psychotherapy alone, no pills

The COMBINE Study

- Percentage of abstinent days per month during a 16-week treatment trial with:
  - Naltrexone 100 mg QD,
  - Acamprosate 1 g TID.

- All treatment groups had an increase in % days abstinent. Overall effect was from 25% to 73%.

The NIAAA COMBINE Study Results

- For patients receiving MM, naltrexone or CBI therapy improved outcomes over placebo plus MM
  - Naltrexone + MM had the best outcome

- Acamprosate did not add benefit to naltrexone or CBI, and was no more effective than placebo plus MM

- Taking tablets and seeing a health care professional was more effective than receiving CBI alone (possible placebo effect)

- One-year outcome: no significant differences among the groups

New Pharmacological Agents

- **Anticonvulsants**
  - Topiramate
  - Gabapentin
  - Carbamazepine
  - Valproic Acid

- **GABA agonist**
  - Baclofen

- **Serotonin (5-HT₃) antagonists**
  - Ondansetron
  - Mirtazapine

- **Selective Serotonin Reuptake Inhibitors**
Conclusions

- Identify the need of your patients to get treatment
- Substance use disorders are chronic, be ready for relapses
- Prevention is based on screening and early Intervention
- CIWA-Ar is your best ally for AWS
- AWS=BZD most effective, safest and cheapest treatment
- Medications for Alcohol Dependence are relatively safe but modestly effective
- Naltrexone is best for “cutting down.”
- Acamprosate is best for preventing “the first drink.”
- Pharmacotherapy and psychotherapy modalities can be offered by you
- Pharmacotherapy and psychotherapy modalities are effective and scientifically based approaches