Alcohol

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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

HISTORICAL VIEW
THE AMERICAN EXPERIENCE

"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 drive 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.

Historical view

Ancient Experience

- Pliny the Elder: Gaius Plinius Secundus
- Naturalis Historia: "drunkenness 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..."

ASAM Disclosure of Relevant Financial Relationships

Content of Activity:
2014 ASAM Review Course

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HISTORICAL VIEW
THE AMERICAN EXPERIENCE

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 (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 19, 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?

NEUROTRANSMITTER SYSTEMS

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Effect</th>
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<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>
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Steps in Synaptic Transmission

Acute Alcohol Intake

Chronic Alcohol Intake
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 $134 billion in productivity
- Causes many other health problems either directly or indirectly

3+ Abuse/Dependence

**ABUSE**

1. **Role failure**
2. **Risk of harm**
3. **Run-ins with law**
4. **Relationship trouble**

In same 12 months

**DEPENDENCE**

1. **Tolerance**
2. **Withdrawal**
3. **Unable to limit**
4. **Unable to cut down**
5. **↑ Time with alcohol**
6. **↓ Time elsewhere**
7. **Use despite problems**

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 2 CRITERIA: NO DIAGNOSIS
- 3 TO 5 CRITERIA: MILD
- 6 TO 8 CRITERIA: MODERATE
- 9 OR MORE CRITERIA: SEVERE

Underdiagnoses 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.
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

**Public Health Approach to Alcohol Use and Disorders**

**SBIRT**

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"
BAC
1 drink $\rightarrow$ BAC $\approx$ 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 mental impairment</td>
</tr>
<tr>
<td>200-299</td>
<td>Very obvious intoxication, except in those with marked tolerance. Nausea, vomiting, marked ataxia</td>
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BAC ↓ by ~15mg%/h

<table>
<thead>
<tr>
<th>BAC mg%</th>
<th>Clinical Manifestations</th>
</tr>
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<tbody>
<tr>
<td>300-399</td>
<td>Hypothermia, severe dysarthria, amnesia, Stage I anesthesia</td>
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<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>
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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)

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>CDT</td>
<td>2–4 weeks of abstinence</td>
<td>1–5 drinks (120g/day) for several weeks</td>
<td>Many sources of false positives—liver disease, smoking, drinking age, anticonvulsants, etc.</td>
<td>M: 0–45 U/L; F: 0–30 U/L</td>
</tr>
<tr>
<td>GGT</td>
<td>2–4 weeks of abstinence</td>
<td>Unknown but heavy</td>
<td>Many sources of false positives (see GGT)</td>
<td>20–90 U/L</td>
</tr>
<tr>
<td>ALT/GGT</td>
<td>2–4 weeks of abstinence</td>
<td>Unknown but heavy</td>
<td>Many sources of false positives (see GGT) same sensitivity as AST</td>
<td>R: 0–7 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>B: 0–100fL</td>
</tr>
<tr>
<td>CDT</td>
<td>2–3 weeks</td>
<td>120g/day for 2 weeks</td>
<td>Few sources of false positives. Good marker of relapse</td>
<td>&lt;40 U/L</td>
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Diagnostic Sensitivity and Specificity of Biomarkers

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
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<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>
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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

- Thiamine
  - Important cofactor for several enzymatic reactions
  - Cerebral glucose utilization
  - Glutamate elimination
- Wernicke's Encephalopathy
  - Partial to complete paralysis of extraocular muscles
  - Nystagmus
  - Ataxia
  - Mental disturbances
  - Mortality: 10-20% if untreated
- 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 catecholamines 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 medical 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
Assessment of Alcohol Withdrawal: CIWA-Ar continued

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

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

Assessment of Alcohol Withdrawal: CIWA-Ar continued

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.

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

Effects of Alcohol on Neurotransmitter Balance

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
Advantages
• No abuse liability
• Cognition
• Neuroprotective
• Protracted Withdrawal

Disadvantages
• Limited clinical experience
• Hematological side effects
• Liver toxicity

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 endogenous opioids are involved in the reinforcing (pleasurable) effects of alcohol and possibly craving
• Prevents a slip from becoming a full-blown relapse

Pharmacotherapy of Alcohol Dependence: Oral Naltrexone 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-150mg 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
  - G1: abdominal pain, decreased appetite, nausea
  - Sedation: daytime sleepiness, fatigue, insomnia, headache
- Reversible hepatotoxicity
  - LFT’s should be monitored closely
- Works best with compliant patients
  - Requires counseling (CBT) or frequent MD monitoring visits (Project Combine, 2006)
  - Efficacy questioned in women (O’Malley, 2007)


![Graph of Naltrexone-Oral in the Treatment of Alcohol Dependence](image)

Naltrexone-Oral in the Treatment of Alcohol Dependence

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<th>Cumulative Proportion with No Relapse</th>
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<tr>
<td>0.1</td>
</tr>
<tr>
<td>Naltrexone (N=35)</td>
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</tbody>
</table>


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)


Pharmacotherapy of Alcohol Dependence: Long Acting Naltrexone (IM)

Results: Heavy Drinking Days

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<thead>
<tr>
<th>Median Heavy Drinking Days per Month</th>
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<tbody>
<tr>
<td>0</td>
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<tr>
<td>Promtreatment</td>
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</tbody>
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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 (creat cl <70ml/min)

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

No drug-drug interactions.

Acamprosate in the Treatment of Alcohol Dependence

Pharmacotherapy of Alcohol Dependence: Disulfiram
Mechanism of Action

- Alcohol → Acetaldehyde → Acetate
- Disulfiram irreversibly binds to acetaldehyde dehydrogenase inhibiting the metabolism of acetaldehyde to acetate.
- Acetaldehyde accumulates resulting in a violent reaction (nausea, vomiting, flushing).
Pharmacotherapy of Alcohol Dependence: Disulfiram Effectiveness

- 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.

Disulfiram and Abstinence Rates (VA Cooperative Study)

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

Combinations

- 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.

Naltrexone/Acamprosate

- 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.

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.