Pharmacotherapy of Alcohol Dependence

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Faculty Disclosure

- Dr. Argo reports she has no actual or potential conflicts of interest associated with this presentation.
- Dr. Argo has indicated that off-label use of medication will be discussed during this presentation.

Epidemiology of Dependence Tx

- Introduction of acamprosate in 2005 → overall alcohol dependence medication sales ~doubled from 2002 to 2007
- Following depot naltrexone marketing, oral naltrexone prescription volume grew
- Number of individuals receiving pharmacotherapy for alcohol dependence continues to be small
  - 2001-2002: 8 million people with alcohol dependence, 705,000 prescriptions filled for ETOH medications (~ 9%)
**Treatment Targets: Where to Begin?**

- Functional dysregulation of neurotransmitters in mesolimbic dopamine system
- Exposure to alcohol or drugs, conditioned cues, multiple genetic factors act together to sensitize
  - Sensitization may lead to neuroadaptation
- Factors influencing behavioral choices
  - Positive reinforcement: reward of intoxication
  - Negative reinforcement: relief from unpleasant symptoms of withdrawal

**Neurochemical Mechanisms of Reinforcement**

- Enkephalin
  - Inhibitory Neuron

- Glutamate
  - Excitatory Input
  - Enkephalin or Dynorphin
  - Inhibitory Neuron

- GABA
  - Inhibitory Feedback

- Ventral Tegmental Area (VTA)
- Nucleus Accumbens (NAc)
- Dopamine Receptors
- GABA-A Receptors
- Presynaptic Opioid (µ, δ, κ) Receptors

**Neurobiology of Alcohol Dependence**

- Glutamate
  - Acute ethanol intoxication → inhibition
    - NMDA R inhibited (↓ glutamate activity)
    - Sedative, incoordinating, amnestic, and anxiolytic effects of alcohol
  - Chronic ethanol intoxication → hypersensitivity
    - Up-regulation of NMDA R number and function
    - Enhancement of NMDA R stimulated intracellular Ca²⁺ levels

- Gamma-aminobutyric Acid (GABA)
  - Acute ethanol intoxication → activation
    - Potentiates GABAₐ inhibition
    - Sedative, incoordinating, amnestic, and anxiolytic effects of alcohol
  - Chronic ethanol intoxication → hyposensitivity
    - Down-regulation of GABAₐ R number and function

- Opioid System
  - Acute ethanol intoxication → activation
    - Endogenous enkephalins release
    - These enkephalins bind presynaptically to µ-receptors on GABAergic neurons
    - Inhibition of GABAergic neurons leads to dopamine release
  - Chronic ethanol intoxication
    - Homeostatic counterbalancing pathways are dampened

- Dopamine (DA)
  - Ethanol activates mesolimbic DA system → increases DA release in nucleus accumbens (NAc)
  - Positive reinforcing and pleasurable effects of ethanol

FDA-Approved Pharmacotherapies

- **Disulfiram- Antabuse ®**
  - Aldehyde dehydrogenase inhibition
  - Dopamine beta-hydroxylase inhibition
- **Naltrexone- Revia ®**
  - Mu (µ) opioid receptor antagonism
- **Acamprosate- Campral ®**
  - Functional glutamate antagonism???

Disulfiram- Antabuse ®: History and Pharmacology

- Approved 1950
- Pharmacology:
  - Acetaldehyde dehydrogenase (ALDH) inhibitor (irreversible)
  - Dopamine beta-hydroxylase inhibition
  - ADH = alcohol dehydrogenase

\[
\text{Ethanol} \xrightarrow{ADH} \text{CH}_3\text{CHO} \xrightarrow{ALDH} \text{CH}_3\text{COOH}
\]

Disulfiram- Antabuse ®: Disulfiram-Ethanol Reaction

- Nausea, vomiting, headache, hypotension, heart attack, flushing, weakness, tachycardia, SOB, sweating, dizziness, blurred vision, confusion
- Anticipation of these symptoms thought to help pts abstain from ETOH
- Reaction, if it develops, will occur within 30-120 min
- Full "protective" effect within 12-14 hrs
- 2 wk wash-out before alcohol interaction abates
- Death can occur from severe disulfiram-alcohol reactions

Disulfiram- Antabuse ®: Treatment Recommendations

- 250mg PO QD
  - range from 125-500mg/d
  - Start when abstinent from ETOH for at least 12 hours
- Predictors of success
  - Motivated
  - Compliant
  - High risk situations
  - Contingencies
  - Supervised administration

Disulfiram- Antabuse ®: RCT evidence

<table>
<thead>
<tr>
<th>Outcomes Measured</th>
<th>Sample Size</th>
<th>Trial Length (wks)</th>
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<tbody>
<tr>
<td># Drinking Days (+) Abstinence (-)</td>
<td>Fuller Roth, 1979</td>
<td>128</td>
</tr>
<tr>
<td># Drinking Days (+) Time to First Drink (-)</td>
<td>Fuller et al., 1986</td>
<td>605</td>
</tr>
<tr>
<td># Drinking Days (+) Ant/Unit Time (-)</td>
<td>Schuckit, 1985 (NR)</td>
<td>348</td>
</tr>
<tr>
<td># Drinking Days (+) Ant/Unit Time (+)</td>
<td>Chick et al., 1992</td>
<td>126</td>
</tr>
</tbody>
</table>
No significant differences among the 3 treatment groups in rate of abstinence or the time to first use. Those with high degree of treatment adherence were the most successful, with 20% of study completers adherent. May benefit those who are motivated.

Disulfiram- Antabuse®: Multisite Veterans Administration Study

- N=605, blinded study, 52 wks
- No significant differences among the 3 treatment groups in rate of abstinence or the time to first use
- Those with high degree of treatment adherence were the most successful
  - 20% of study completers were adherent
- May benefit those who are motivated

Naltrexone-Revia®, Vivitrol™: History and Pharmacology

- Approval 1994
- Pharmacology:
  - Competitive mu (µ) opioid receptor antagonist
    - Naltrexone blocks β-endorphin
      - Alcohol ingestion activates β-endorphin which stimulates dopamine release
      - Naltrexone blocks ethanol-induced DA release in NAc
        - May attenuate rewarding effects of alcohol

Naltrexone-Revia®, Vivitrol™: Treatment Recommendations

- Dose
  - Standard dose: 50mg/d (oral)
  - Vivitrol™ 380mg/monthly (SQ or IM)
- Side effects
  - Usually well-tolerated
    - Nausea (10%)
    - Headache (7%)
    - Dizziness (4%)
    - Fatigue (4%)
  - Reversible elevation in LFTs
    - Watch LFTs if use with other drugs that are known to cause liver toxicity e.g. disulfiram or acetaminophen
    - Clarify no concomitant opiate abuse before initiation

Naltrexone-Revia®, Vivitrol™: Meta-analyses, Short-Term Use

- Carmen, 2004
  - Reduction of relapse rate: OR = 0.62 (0.52, 0.75); N=1142
  - No better abstinence rate: OR = 1.26 (0.97, 1.64); N=544
- Srisurapanont and Jarurassiraisin, 2005
  - Reduction of relapse rate: RR = 0.64 (0.51–0.82); N=415
  - No better in return to drinking: RR = 0.91 (0.81–1.02); N=459
- Roozen, 2006
  - Difference in relapse rate: RD = 13% (7%, 18%); N=949
  - No difference in cumulative abstinence: RD = 6% (2%, 15%); N=396

Naltrexone-Revia®, Vivitrol™: Meta-analyses, Longer-Term Use

- Long-term effectiveness ???
  - One study: beneficial effects diminish gradually over time
  - One study of LAI has shown effects sustained during 6 months of treatment
- Roozen, 2006
  - No better in % drinking days: WMD = 2.75 (2.36 to 7.86); N=452
Acamprosate-Campral®
History and Pharmacology

- FDA approved (2004)
  - Approved to maintain abstinence after detoxification
- MOA
  - Unknown
  - "Restores balance" between glutamate and GABA
  - May ↓ glutamate overactivity
  - Binding to allostERIC polyamine site on NMDA R and ↓ polyamine
  - May ↓ ability of ethanol to activate mesolimbic dopamine system

Acamprosate-Campral®
Treatment Recommendations

- Dose
  - Standard dose: 666mg PO TID
  - Moderate effects
  - Majority of trials European
- Long-term effectiveness
  - In long-term trials, 16-30% of subjects completely abstinent at 48 and 52 week endpoints

Acamprosate-Campral®
Treatment Recommendations

- Side effects
  - Only ADR reported in >10% patients and at a rate > placebo was transient diarrhea
    - Asthenia (6%)
    - Anxiety (6%)
    - Insomnia (7%)
- Renally eliminated
  - Should not be used if CrCl < 30
- Considered safe to use with medications commonly used in alcohol dependence

Acamprosate-Campral®
Meta-analyses, Short-Term Use

- Carmen, 2004
  - Improved abstinence rate: OR = 1.88 (1.57, 2.25); N=1775
  - Improved cumulative abstinence: WMD = 26.55 (17.56, 36.54); N=1195
- Mann, 2004
  - Improved cumulative abstinence: RB = 1.47 (1.29, 1.69); N=2,160
- Cochrane Collaboration, 2011
  - Reduced risk of any drinking: RR = 0.86 (0.81, 0.91); N=3,233
  - Increased cumulative abstinence duration: MD = 10.94 (5.08, 18.81); N=2,763

Combination Treatment
Disulfiram + Acamprosate

- RCTPC, 52wks, N=118
  - Voluntary intake of DSF (dose = ??)
  - DB randomization to acamprosate or placebo
- Follow-up for additional 52 wks
  - Only 18 pts completed 164 wk study period

Combination Treatment
Disulfiram + Acamprosate

- RR: ACAM > PLB through 38 wks
- CAD: ACAM > PLB over 52 wk tx period
  - Concomitant disulfiram improved effectiveness of ACAM

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<tr>
<th></th>
<th>CAD (days)</th>
<th>SD</th>
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<tbody>
<tr>
<td></td>
<td>over 52 wk tx</td>
<td></td>
</tr>
<tr>
<td>All Patients</td>
<td>Placibo</td>
<td>74.7</td>
</tr>
<tr>
<td></td>
<td>ACAM</td>
<td>136.9</td>
</tr>
<tr>
<td>+ DSF</td>
<td>Placibo</td>
<td>111.8</td>
</tr>
<tr>
<td></td>
<td>ACAM</td>
<td>185</td>
</tr>
<tr>
<td>No DSF</td>
<td>Placibo</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>ACAM</td>
<td>99.7</td>
</tr>
</tbody>
</table>

Combination Treatment/Head-to-Head
Disulfiram + Naltrexone

- CDA: Combo = Mono; DSF = NTX; Any med > PLB
- % DA: Combo = Mono; DSF = NTX; Any med = PLB
- % HDD: Combo = Mono; DSF = NTX; Any med = PLB
- % TA: Combo = Mono; DSF = NTX; Any med = PLB


Combination Treatment
COMBINE Study: Naltrexone + Acamprosate

- 9 arm study, NIAAA supported
- Combinations of 3 interventions (NTX 100mg/d, ACAM 3gm/d, behavioral) and PLB x 16 wks
- Pt evaluated for up to 1 yr


Combination Treatment
COMBINE Study: Naltrexone + Acamprosate

- % days abstinent
  - No significant main effects of ACAM, NTX, or CBI
  - NTX x CBI interaction was significant
    - Those receiving either NTX or CBI had the most abstinent days
    - Those neither receiving NTX or CBI had the fewest abstinent days
    - Combined therapy with NTX + CBI had no additional benefit over NTX alone or CBI alone
    - NTX vs. PLB in absence of CBI: effect size = 0.22


Combination Treatment
COMBINE Study: Naltrexone + Acamprosate

- Time to first heavy drinking day
  - No significant main effects of ACAM or CBI
  - Significant main effect of NTX: HR = 0.72
  - In context of MM:
    - Those receiving NTX without CBI had the longest time to FHDD
    - CBI + NTX and CBI + PLB were intermediate
    - Those neither receiving NTX or CBI had the shortest time
    - NTX vs. PLB in absence of CBI: HR = 0.78


Combination Treatment
COMBINE Study: Naltrexone + Acamprosate

- Secondary endpoints:
  - Craving (OCDS): NTX (9.7) better than PLB (10.9)
  - Good clinical outcomes:
    - MM + PLB: 58%
    - MM + NTX: 74% (NNT = 6)
    - MM + CBI + PLB: 71% (NNT = 7)
    - MM + NTX + CBI: 74% (NNT = 6)


Combination Treatment
COMBINE Study: Naltrexone + Acamprosate

- Secondary endpoints:
  - CBI with/without pills, i.e. "placebo effect"
    - MM + PLB vs CBI better than CBI alone (no pills or MM) in regards to % days abstinent
    - MM + PLB vs CBI better than CBI alone (no pills or MM) in regards to relapse rate into heavy drinking
  - Posttreatment follow-up (1 yr)
    - Trend for CBI-treated to have higher % days abstinent over any medication group
    - NTX-treated "nominally" less risk of returning to at least one heavy drinking day over time
Combination Treatment/Head-to-Head
Naltrexone + Acamprosate

- RCTDBPC, 12wks, N=160
  - NTX 50mg/d, ACAM 1998mg/d
- Nonrelapse rates to heavy drinking & time to first drink
  NTX > PLB  NTX = ACAM
  ACAM > PLB  NTX + ACAM > ACAM
  NTX + ACAM > PLB  NTX + ACAM = NTX


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Combination Treatment/Head-to-Head
Naltrexone + Acamprosate

- RCTSB (investigator-blinded), 52wks, N=157 males
  - Naltrexone 50mg/d, acamprosate 1665-1998mg/d
- Primary outcomes:
  - Time to first relapse: NTX (63 d) > ACAM (42 d)
  - CDA: NTX (243 d ±115) > ACAM (180 d ±129)
- Secondary outcomes:
  - Mean time to first drink: NTX (44 d) = ACAM (39 d)
  - Craving severity (composite of 3 scales): NTX > ACAM
  - % not relapsed at 1 yr: NTX (41%) > ACAM (17%)


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Combination Treatment/Head-to-Head
Naltrexone + Acamprosate

- RCTDBPC, 12wks, N=169 males
  - PLB (24.6)= NTX (24.3) = ACAM (24.1)
  - Time to first drink (days): PLB (33.4) = NTX (39.2) = ACAM (33.6)
  - CAD (days): PLB (56.7) = NTX (57.8) = ACAM (66.3)
- Secondary outcomes:
  - Craving (PACS score/30) : PLB (10.9) = NTX (11.1) = ACAM (10.9)

Off-Label Therapies

- Pharmacologic Mechanisms of Action:
  - Serotonin reuptake inhibition
  - 5HT3 antagonism
  - Dopamine antagonism
  - GABA-B agonism
  - Potentiation of GABA signaling
  - α1 adrenergic antagonism

SSRIs

- Fluoxetine 60mg/d, RCTDBPC, 12wks, N=101
  - No differences in active tx vs. PLB in drinking outcomes
  - Type B alcoholics may have worsened with active tx
- Sertraline 200mg/d, RCTDBPC, 14wks, N=100
  - ↓ drinking in those w/ comorbid MDD
  - Subgroup analysis:
    - Type A alcoholics: ↓drinking
    - Type B alcoholics: worsening drinking

Combination Treatment

Sertraline + Naltrexone: Mixed findings

- In pts with co-occurring depression, OR=3.7 for abstinence at 14 wks with combo over either monotherapy
- Another study (16 wks) in rural, non-depressed Alaska natives combo = NTX for abstinence rates and other secondary drinking outcomes
- Recent 12 wk study confirmed same findings (combo – NTX) in non-depressed pop (N=113) in outcomes of time to first drink time to relapse to heavy drinking

Ondansetron

Clinical Trial Evidence

- Ondansetron 0.25mg BID or 2mg BID, RCTDBPC, 6 wks, N=71 (males)
  - ↓ drinks/day (EOA) & ↓ drinks per drinking day (EOA)

Combination Treatment

Ondansetron + Naltrexone

- Small RCTDBPC, 8 wks in EOA showed effectiveness of OND + NTX vs. PLB
  - Mean 1 drink/day vs. 3.7 drinks/day in PLB
  - 1 of four subscales of the obsessive compulsive drinking scale (measuring craving) significantly lower scores in combo vs. PLB
  - However, no NTX monotherapy tx group to compare outcomes
### Dopamine Antagonists
**Clinical Trial Evidence**

- Aripiprazole, up to 30mg/d, RCTDBPC, 12 wks, N=295
  - Negative study
  - Mean % days abstinent were similar (58.7% vs. 63.3%)
  - ARP group: more ADRs, study discontinuation
- Haloperidol, olanzapine, and quetiapine also have study

### Baclofen
**Clinical Trial Evidence**

- Baclofen 30mg/d, RCTDBPC, 4 wks, N=39
  - ↑ CAD
  - ↓ craving
  - Findings were duplicated in a separate study with liver cirrhosis population
- Baclofen dose 30mg/d, RCTDBPC, 12wks, N=80
  - Negative study
  - No differences in % heavy drinking days, craving, % days abstinent, time to first drink, or time to relapse into heavy drinking

### Potentiation of GABA signaling
**Clinical Trial Evidence**

- Topiramate, up to 300mg/d, RCTDBPC, 12 wks, N=150
  - ↓ # drinks consumed/day: 2.88 (-4.50 to –1.27)
  - Fewer drinks per drinking day: 3.10 (-4.88 to –1.31)
  - ↓ total days abstinent (26.2%)
  - Improved craving
- Topiramate, up to 300mg/d, RCTDBPC, 14 wks, N=371
  - ↓ heavy drinking days: 16.19% (10.79% to 21.60%)
  - ↓ craving
  - ↑ physical health

### Future Mechanistic Targets

- CB1 antagonism
- mGluR5 antagonism
- mGluR2/3 agonism
- Corticotropin releasing factor
- Neuropeptide Y
- Nociceptin
- Neurokinin receptors/Substance P
- Ghrelin

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Anton RF et al., 2008. J Clin Psychopharmacol, 28(1):5-12

Johnson BA et al., 2007. JAMA, 298:1641-51