Pharmacotherapies for Alcohol Dependence
Current and investigative approaches

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Disclosures

BLF and SL are supported by CAMH

Dr Le Foll’s research support:
CAMH
Ontario Ministry of Innovation
Canadian Fondation for Innovation,
Canadian Tobacco Control Research Initiative
Pfizer GRAND Award 2008, 2009, 2010
Pfizer Cardio-vascular Research Award
CIHR training program
OPGRC
Ontario Lung Association
Heart and Stroke Foundation
NIH-NIDA
Goal and Objectives

Goal

- To understand the role of pharmacotherapy in the treatment of alcohol dependence

Objectives

- Knowing the current data on the epidemiology of alcohol dependence
- Understanding alcohol dependence as a brain disorder
- Being familiar with current and emerging pharmacotherapies for alcohol dependence
Epidemiology

- Among the main leading health-risk factor in most countries (Alonso, 2004)
- Causes 20-30% of esophageal cancer, liver disease, epilepsy, motor vehicle accidents, homicide and other intentional injuries (WHO, 2002)
- 2004: 3.8% of all global deaths and 4.6% of global disability-adjusted life-years were attributable to alcohol (Rehm, 2009).
Epidemiology

- Estimated economic cost to society: $185 billion/year (Harwood, 2000)
  - More than nicotine and illicit drugs
- Alcohol use is the second leading cause of disability in the US and Canada among individuals 15-44 years old (WHO, 2002)
- Only 10% of individuals with alcohol dependence receive the recommended care (McGlynn, 2003)
12-month prevalence of alcohol and drug dependence

<table>
<thead>
<tr>
<th>Substance</th>
<th>%</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>3.8</td>
<td>0.14</td>
</tr>
<tr>
<td>Sedative</td>
<td>0.07</td>
<td>0.01</td>
</tr>
<tr>
<td>Tranquilizer</td>
<td>0.05</td>
<td>0.01</td>
</tr>
<tr>
<td>Opioids</td>
<td>0.11</td>
<td>0.02</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>0.07</td>
<td>0.02</td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>Cannabis</td>
<td>0.32</td>
<td>0.04</td>
</tr>
<tr>
<td>Cocaine</td>
<td>0.13</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Stinson, 2005
Diagnosis – Alcohol dependence

Three (or more) of the following within a 12-month period:

- Tolerance
- Withdrawal
- Alcohol is consumed in larger amounts or over a longer period than was intended
- There is a persistent desire or unsuccessful efforts to cut down or control alcohol use
- A great deal of time is spent in activities necessary to obtain alcohol, use alcohol or recover from its effects
- Important social, occupational, or recreational activities are given up or reduced because of alcohol use
- Alcohol use is continued despite knowledge of its negative physical or psychological effects
Diagnosis – Alcohol withdrawal

- Two (or more) of the following, developing within several hours to a few days after cessation or reduction in alcohol use that has been heavy and prolonged
  - autonomic hyperactivity (e.g., sweating or pulse rate greater than 100)
  - increased hand tremor
  - insomnia
  - nausea or vomiting
  - transient visual, tactile, or auditory hallucinations or illusions
  - psychomotor agitation
  - anxiety
  - grand mal seizures
Screening tools

- **Single question**
  - “On any single occasion during the last 3 months, have you had more than 5 alcoholic drinks?” (Taj, 1998)

- **CAGE questionnaire** (2 or more positive answers):
  - Have you ever felt you should **cut down** on your drinking?
  - Have people **annoyed** you by criticizing your drinking?
  - Have you ever felt bad or **guilty** about your drinking?
  - **Eye opener**: Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover?
AUDIT

- Alcohol Use Disorders Identification Test
- Developed by WHO
- 10 questions
  - Amount and frequency of drinking: 3 questions
  - Alcohol dependence: 3 questions
  - Problems caused by alcohol: 4 questions
- Score of 8 or more – problem drinking
Standard Drinks (SD)

- In Canada, one SD = 13.6% of alcohol
- Examples of 1 SD:
  - 341 ml (12 oz) of beer or cooler (5%)
  - 142 ml (5 oz) of table wine (12%)
  - 85 ml (3oz) of fortified wine (sherry, port - 16%)
  - 43 ml (1.5 oz) of spirits (40%)
Alcohol and the Brain - chronic alcohol consumption

- Alcohol works via the GABA-A receptor, increasing influx of chloride and cellular hyperpolarization
- Chronic alcohol consumption results in “hyperactive” GABA activity and consequent down-regulation of post-synaptic receptors
- Concurrently, chronic alcohol consumption results in “hypoactive” glutamate activity and consequent up-regulation of post-synaptic receptors
Alcohol and the Brain - alcohol withdrawal

- Alcohol withdrawal results in a sudden drop in GABA levels and a surge in glutamate levels.
- These effects, combined with the down-regulation in GABA receptors and up-regulation of glutamate receptors cause “hyperactive” glutamate activity and “hypoactive” GABA activity.
- These changes in neurotransmitter activity may cause seizures and autonomic instability (i.e. Delirium Tremens).
Alcohol and the Brain – downstream effects

- The effects of alcohol are also transmitted via the activity of alcohol on opioid-receptors in the brain.
- Accordingly, GABA, glutamate and opioid receptors are targets for pharmacotherapy of alcohol-dependence.
Alcohol also targets endogenous opioids
Downstream effect: elevation of dopamine
Addicted Brain signature

Dopamine D2 Receptors are Lower in Addiction

Adapted from Volkow et al., Neurobiology of Learning and Memory 78:610-624, 2002.
Treating alcohol dependence

- Phase I – detoxification (in or out-patient)
  - Using Diazepam (or Lorazepam in cases of liver dysfunction)
- Phase II – Relapse prevention
- Psychotherapy:
  - Motivational Interviewing
  - 12 step facilitations
  - Cognitive-Behavioral therapy

Despite these effective psychotherapies, 40-70% relapse within one year after psychosocial treatment (Finney, 1996).

Additional treatment modalities for relapse prevention are needed
Medications tried in alcohol dependence

- **Dopaminergic**
  - Tiaprid
  - Amisulpride
  - Flupentixol

- **Serotonergic**
  - Buspirone
  - Fluoxetine
  - Nefazodone
  - Ritanserin

- **Mood Stabilizers**
  - Lithium
  - Carbamazepine

- **Sedatives**
  - Benzodiazepines

- **Cholinergic**
  - Galantamine

- **Others….**
Current pharmacological treatments for alcohol dependence

- Benzodiazepines (for acute alcohol withdrawal)
- Disulfiram (Antabuse®)
- Naltrexone (Revia®)
- Acamprosate (Campral®)
- Topiramate (Topamax®)
- Baclofen (Lioresal®)
Disulfiram

- Inhibits the metabolism of alcohol
- Individuals develop a severe adverse reaction when exposed to alcohol, and develop aversion (via operant conditioning) and “fear” of drinking alcohol

![Diagram showing the metabolism of alcohol](image)
Disulfiram – cont.

- Standard dose = 250-500 mg/d
- Common adverse effects include:
  - Drowsiness
  - Metallic taste
  - Hepatotoxicity
  - If alcohol is consumed – flushing, palpitations, headache, respiratory depression, CV collapse, seizures, death
Disulfiram is much more effective when it is monitored

<table>
<thead>
<tr>
<th>Author, Yr</th>
<th>Follow-up</th>
<th>Disulfiram</th>
<th>Abstinence</th>
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</thead>
<tbody>
<tr>
<td>Gerrein, 1973</td>
<td>85%, 39%</td>
<td>Monitored</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unmonitored</td>
<td>7%</td>
</tr>
<tr>
<td>Azrin, 1976</td>
<td>90%</td>
<td>Monitored</td>
<td>90-98%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unmonitored</td>
<td>55%</td>
</tr>
<tr>
<td>Azrin, 1982</td>
<td>100%</td>
<td>Monitored</td>
<td>73%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unmonitored</td>
<td>47*</td>
</tr>
<tr>
<td>Liebson, 1978</td>
<td>78%</td>
<td>Monitored</td>
<td>98%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unmonitored</td>
<td>79%</td>
</tr>
</tbody>
</table>

Length of follow-up was as follows: Gerrein 1973: 8 weeks; Azrin 1976: 2 years, Azrin 1982: 6 months; Liebson 1978: 6 months. * Thirty-day abstinence at 6 months
Positive outcomes of disulfiram treatment are associated with (Hughes, 1997):

- Age > 40
- Long standing alcohol drinking
- Socially stable
- Attending AA
- High motivation
- Cognitively intact
- Monitored

Disulfiram can be given on a “as needed” basis (i.e. before a party)

Disulfiram is not manufactured today in Canada, can be supplied through special pharmacies.
Naltrexone

- An Opioid antagonist
- Approved for treating alcohol dependence
- Standard dose = 50 mg/d (once daily)

Common adverse effects:
- Nausea
- Headache
- Depression
- Dizziness
- Fatigue
- Insomnia
- Anxiety
- Sleepiness
Naltrexone is more effective than placebo in reducing relapse rates

O’Malley, 1992
Naltrexone – cont.

- Is not appropriate for individuals taking opiates
- Is not appropriate if liver enzymes (ALT, AST) are more than 2-3 times the norm
- Liver enzymes should be monitored 2-3 weeks after treatment is initiated
- Continue treatment for at least 3-6 months
Naltrexone – Cochrane meta-analysis

Opioid antagonists [naltrexone] for alcohol dependence (Rosner, 2010)

- 50 studies, 7793 subjects
- Naltrexone is more effective than placebo: reduces the risk of heavy drinking and decreases number of drinking days, amount of alcohol consumed and gamma-glutamyltransferase levels.
- Safe treatment (CI if opiates)
- Injectable depots may be as effective as oral med. (Vivitrol, approved in the US, not yet in Canada. Implants for one year recently developed)
Acamprosate

- NMDA antagonist
- decreases glutamate levels during withdrawal
- Approved for treating alcohol dependence
- Standard dose = 666 mg tid
- Common adverse effects:
  - Diarrhea
  - Rash, itching
  - Change in sexual desire
  - Dizziness
  - Headache
  - Insomnia
Acamprosate – Cochrane meta-analysis

- **Acamprosate for alcohol treatment** (Rosner, 2010)
  - 24 studies, 6915 subjects
  - Acamprosate is more effective than placebo: significantly reduces the risk of any drinking and significantly increases the cumulative abstinence duration
  - Safe treatment (diarrhea more common than placebo)
Topiramate

- Facilitates GABA function through GABA-A receptors
- Antagonist of glutamate receptors (AMPA/Kainate)
- Experimental treatment for alcohol dependence; has been shown to be effective in 4 large clinical trials (Johnson 2003, Johnson 2004, Johnson 2007, Johnson 2008)
Topiramate – cont.

- Adverse effects:
  - Skin numbness or tingling
  - Difficulty with concentration or attention
  - Nervousness
  - Difficulty with memory
  - Drowsiness
- Doses must be titrated gradually
# Topiramate - titration

<table>
<thead>
<tr>
<th>Week</th>
<th>AM dose</th>
<th>PM dose</th>
<th>Total daily dose</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>50</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>100</td>
<td>150</td>
</tr>
<tr>
<td>6</td>
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<td>7</td>
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<td>150</td>
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<tr>
<td>8</td>
<td>150</td>
<td>150</td>
<td>300</td>
</tr>
</tbody>
</table>
Baclofen (Lioresal®)

- GABA-B Agonist
- Approved as a myorelaxant
- Experimental treatment for alcohol dependence; has been shown to be effective in one large clinical trial
- Standard dose = 10-20mg tid
Common adverse effects:
- Drowsiness
- Headache
- Nausea
- Low blood pressure
- Constipation
- Confusion
- Insomnia
Bottom line – what medication should be chosen?

- Disulfiram – potentially severe adverse effects, requires high motivation, preferably monitored
- Naltrexone prevents heavy drinking and maintains abstinence; better in preventing a lapse from becoming a relapse
- Acamprosate maintains abstinence, better in preventing a lapse
- Topiramate has promising results but not formally approved yet
- Baclofen: unclear, perhaps higher doses are needed
Case #1

- A 43 year old man reports consuming 12 cans of beer (333ml each) per day for the past 8 years. He usually starts drinking the late afternoon and drinks throughout the evening. He does not report any additional medical problems and denies suffering from seizures during previous quitting attempts.
Case #1 – cont.

- What diagnostic tests should be conducted in order to assist in deciding upon the appropriate medication?
- What medication/s would be an appropriate first line treatment for this client?
Case #2

- A 60 year old woman has been drinking one mickey (12 oz) of scotch per day for the last 5 years. She reports daily withdrawal symptoms in the morning – agitation, anxiety, tremor. Her liver enzymes have been found to be elevated (AST=138, ALT = 181).
Case #2 – cont.

What medication/s would be an appropriate first line treatment for this client?
Some of the challenges

- Physicians often do not screen and do not diagnose
- Perception that there is no effective treatment
- Clients are not aware of treatments options beside AA and Antabuse
- Medications are not on formulary/ Dug Cost
- Limited number of physicians interested in treating the disorders
- Limited integration between the psycho-social interventions and the medical interventions
- ALCOHOL CLINIC AT CAMH WAS ESTABLISHED TO ADRESS THESE BARRIERS
Alcohol Dependence Clinic

- What we offer
  - Outpatient withdrawal management (Day Detox)
  - Medication prescribing for alcohol use disorders
  - Counselling & case management
  - Concurrent treatment for mood and/or anxiety by psychiatrists
  - Referral to internal and external support services
  - On-site resource room offering information and support
  - Education and training for health professionals
  - Opportunities to participate in Research Studies on a voluntary basis
Conclusions of the presentation

- High prevalence and limited use of treatment (it is cost effective)

- We are starting to understand the addicted brain (GABA, glutamate, opioid and DA alterations are proven)

- We are moving toward evidence-based approaches that will directly target the disease process

- We need to use sequential approaches to identify what treatment works best until we find a better way

Adapted from Le Foll, 2007 *CMAJ*
Acknowledgements

**Translational Lab**
Yann Le Strat
Saul Lev Ran
Farid Araki, Keyghobad Gamaladdin, Islamhany Khaled, Maram Pushparaj, Abhiram Genane Loheswaran Mihail Guranda Greg Staios

**Genetic**
James Kennedy
Daniel Mueller

**Clinical Programs**
Peter Selby
Tony George

**PET Centre**
Alan Wilson
Isabelle Boileau
Sylvain Houle

**Social and Epidemiology**
Jurgen Rehm

Administrative support
Dennis James
Chris Bartha

**All Addiction Medicine Service staff/Fellows**
Wendy Fenomeno
Lisa Lefebvre
Kam Balchand

**Pharmacy Staff**
NIH for slides