Reducing excessive alcohol use and harm in Alaska.
Medication Assisted Treatment for Alcohol Use Disorder: Current Status and Future Directions

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Dr. Mason has no conflicts of interest to disclose
Cost and Scope of Substance Use Disorder

### Prevalence
- **Alcohol**: 16.7 million
- **Tobacco**: 22.9 million
- **Stim/opiate/MJ**: 7.6 million
- **Cancer**: 13 million
- **HIV/AIDS**: 1.1 million

### Cost to Society
- **Alcohol**: $223 billion
- **Tobacco**: $155 billion
- **Stim/opiate/MJ**: $161 billion
- **Cancer**: $202 billion
- **HIV/AIDS**: $36 billion

### Deaths
- **Alcohol**: 75,000 deaths
- **Tobacco**: 443,000 deaths
- **All illicit drugs**: 17,000 deaths
- **Cancer**: 580,000 deaths
- **HIV/AIDS**: 15,000 deaths

### NIH Budget
- **Alcohol**: $460 million
- **Tobacco**: $359 million
- **Drug Abuse**: $1,072 million
- **Cancer**: $5671 million
- **HIV/AIDS**: $3122 million

Source: NIH, CDC
What is Alcohol Use Use Disorder?

DSM V = 2 of 11 sx, moderate+ severity = 4+ sx
Also called:
• Alcohol Addiction
• Alcohol Dependence (DSM IV, ICD 10, draft ICD 11)
• Alcoholism

Defined as a chronic, relapsing disorder that involves:
• Compulsive alcohol seeking and drinking
• Loss of control over drinking
• Tolerance and physiological withdrawal
• A protracted *motivational* withdrawal syndrome
  - negative emotional state (dysphoria, anxiety, irritability)
  - sleep disturbance
Current Status of Pharmacotherapies for Alcohol Use Disorder

FDA-approved medications are limited

- disulfiram (Antabuse), 1951, FDA-approval
- naltrexone (ReVia, Vivitrol), 1994, 2006, FDA-approval
- acamprosate (Campral), 2004, FDA-approval

FDA-approved medications are under-utilized

- Prescribed for < 9% of 8.4m Americans with alcohol use disorder

Relapse rates are high following non pharmacological treatment

- 80% relapse 1+ times during year following treatment
FDA-approved Medications for AUD

**Disulfiram**
(Antabuse)
125-500mg orally
$18/month generic
FDA approved in 1951

- **Mechanism:** the alcohol-disulfiram interaction
  - Inhibits the metabolism of alcohol
  - Acetaldehyde quickly builds up
  - Rapid onset of flushing, nausea and palpitations
  - A psychological deterrent to alcohol use

- **Efficacy**
  - Medication compliance tends to be poor
  - Optimized with supervised administration and compliant participants who want to quit drinking completely

- **Safety**
  - Should not be given to someone in a state of alcohol intoxication, or without their full knowledge.
  - Hepatotoxicity, drowsiness
FDA-approved Medications for AUD

Naltrexone (Revia, generic)
50mg orally, $27/month
FDA approved 1994

Mechanism
• A pure opioid receptor antagonist
• If alcohol consumption is less rewarding, drinking will decrease.

Efficacy
• Increases rates of no heavy drinking (NNT = 8.6 - 12)
• Compliance problems with oral daily dosing
• Vivitrol once-monthly extended-release intramuscular injection

Safety
• Do not give to patients with current prescribed or illicit opiate use, as it will induce acute opioid withdrawal.
• Hepatotoxicity

Naltrexone (Vivitrol)
380mg extended-release Injectable, FDA approved 2006
$1372/month
FDA-approved Medications for AUD

**Mechanism**
- Heavy drinking and withdrawal dysregulate the balance between neuronal excitation (glutamatergic) and inhibition (GABAergic).
- Restores homeostasis in NMDA-mediated glutamatergic neurotransmission.

**Efficacy**
Increases rates of abstinence in studies up to 1 year long (NNT = 7.5 - 12)

**Safety**
- Not metabolized in the liver, excreted renally
- Safe in patients with hepatic impairment.

**Acamprosate**
(Campral)
1998mg orally
$108/month
FDA approve 2004
When, How, What Drug to Prescribe to Treat AUD: Disulfiram, Acamprosate, Naltrexone?

- Consider medication especially if there is an inadequate response to counseling
- Review package insert, NIAAA Clinician’s Guide, talk with colleague
- Review drug pros and cons with patient, keeping in mind their health status, motivation to be abstinent, and their preference
- In case of inadequate response, meds may be used sequentially or in combination, and can be restarted in case of relapse
FDA-approved drugs to treat AUD have the following characteristics:

• Not a cure
• Not alcohol-substitution drugs
• Not addictive or habit forming
• Should be prescribed in conjunction with counseling
• Have better drinking outcomes (with counseling) than placebo (with counseling)
• Efficacy higher with initial abstinence: 4-7 days
Study of Investigational Drugs in Humans Requires an Investigational New Drug (IND) Application Accepted by the FDA

An IND contains data to determine if a drug is safe to test in humans and includes:

– Animal, pharmacology and toxicology studies
– Chemistry and manufacturing info
– Clinical protocols, Investigator credentials, Informed Consent and IRB approval

Also required for:
– New Indication
– Change in approved route of administration or dose
– Change in approved patient population
Clinical Studies Required for Regulatory (FDA) Approval of an Experimental Drug

Phase I: assesses safety and pharmacokinetics (absorption, metabolism, excretion) in healthy paid volunteers, across a range of doses (~30% failure rate)

Phase II: assesses safety and efficacy in patients with the indicated disorder, using randomized, double-blind, placebo-controlled trials (RCTs) involving up to several hundred patients (~66% failure rate)

Phase III: 6-month RCTs involving several hundred to 1000s of patients (10 - 30% failure rate)

Post-marketing Surveillance (Phase IV) Trials are conducted after drug approval
Measures of Alcohol Consumption

Patient Reported Outcomes
– Timeline Follow-Back Interview
  Calendar-based retrospective estimates of daily drinking
  Psychometrically evaluated and field tested
– Ecological Momentary Assessment (EMA)

Objective Outcomes
– Direct measures: BAC, alcohol glucuronide
– Indirect measures: GGT, CDT
– Biosensors
Abstinence outcome: Not a single drink during a 6-month RCT or after a pre-specified grace period

Each Contains the same amount of Alcohol (0.6 oz)*

*US Dietary Guidelines
Heavy Drinking Outcome

Binge Drinking: BAC reaches 0.08g/dL within 2 hours

≥ 4/Day
≥ 7/Week

≥ 5/Day
≥ 14/Week
Drug Targets by Stage of the Alcohol Use Disorder Cycle with Corresponding Clinical States

**Binge Intoxication**
- Disulfiram
- Naltrexone
- Reward Modulators
  - Dopamine
  - Opioid
  - Receptor channels

**Preoccupation**
- Acamprosate
- Glutamate
  - AMPA
  - Metabotropic
  - NMDA
- Molecular Cellular
  - Transcription factors
  - Translation factors

**Anticipation**
- Prefrontal Cortex
- Basal Ganglia
- Extended Amygdala

**Withdrawal**
- Negative Affect

**Brain Stress Systems**
- CRF
- Dynorphin
- Glucocorticoid
- Hypocretin
- Norepinephrine
- Vasopressin

**Neuroimmune Brain Anti-stress Systems**
- Endocannabinoid
- Neuropeptide Y
- Nociceptin
- Oxytocin

Medications Development for Treatment of Alcohol Use Disorder

Koob GF, Lloyd GK, Mason BJ. Nat Rev Drug Discovery 2009; 8:500
Grant number R01 AA012602; 1999 – present
The aim is to restore neurocircuitry changes in the pathophysiology of alcoholism to within a homeostatic range of functioning, i.e., block the recruitment of brain stress systems that drive negative reinforcement and provide a powerful motivation for relapse to drinking.

1. A systematic preclinical evaluation of the most promising small molecules directed at neurobiological targets for the Withdrawal Negative Affect and Preoccupation Anticipation stages of protracted withdrawal.

2. Clinical testing of compounds with a similar mechanism of action and an IND using:
   a) Proof-of-concept human laboratory studies
   b) Randomized clinical trials
Human Lab Model of Protracted Withdrawal

Method: Affective priming, in vivo exposure to alcohol

Subjects: Non treatment-seeking males and females with alcohol dependence, abstinent 3 days prior to testing

Design: Double-blind, placebo-controlled, random assignment, dosing based on PK, typically 1-week

Primary outcome: Visual Analogue Scale - craving
  ▪ Confirmatory outcomes: EMG, heart rate, GSR
  ▪ Exploratory outcome: sleep, mood, cognition

Safety: Physical exam, labs, vital signs, SAFTEE, ARCI
Mood Induction Methods

- Affective images were selected from the International Affective Picture System (IAPS; CSEA, 1994).
- Images are presented on a monitor in a digitized format.
- 12 images with similar emotional content are presented over a 3 minute period.
- Subjects are asked to look at each picture and try to feel the mood evoked by the picture.
Beverage Cue Exposure Procedures

• The subject’s preferred alcoholic beverage or bottled water are presented in random order for 90 seconds following each mood condition.

• The subject is told to hold and sniff the beverage for 90 seconds and to not drink it.
Primary Outcome: Craving VAS Items*

1. How strong is your craving to drink alcohol? **STRENGTH**
2. If I could drink alcohol now, I would drink it. **IMPULSE**
3. It would be hard to turn down a drink right now. **CONTROL**
4. Having a drink would make things just perfect. **RELIEF**

* 0 = None, 20 = Extremely Strong
Convergence of Mason Human Lab Results with Drinking Outcomes in AUD Randomized Clinical Trials

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Summary of Human Lab Model of Protracted Abstinence

• Uses mood induction and *in vivo* alcohol cues

• Reliably causes craving in abstinent alcoholics

• Decreased drinking is predicted by decreased alcohol-induced craving in the human laboratory model

• Demonstrated predictive validity for drinking outcomes in clinical trials of acamprosate, naltrexone, gabapentin, pregabalin and duloxetine in alcoholics

• Offers a reliable method for POC testing of drugs to treat relapse risk in protracted abstinence in alcohol dependence
Gabapentin
Rationale for Gabapentin (Neurontin) as a Treatment for Alcohol Use Disorder

- FDA-approved for epilepsy and pain
- Associated with modulation of GABAergic activity via action on voltage-gated calcium channels
- Hypothesized to functionally restore homeostasis in brain stress systems dysregulated in protracted abstinence
- Used off-label to treat symptoms associated with protracted abstinence and risk of relapse
  - Depression
  - Anxiety
  - Insomnia: Decreased stage 1 sleep and arousals, increased slow wave sleep and sleep efficiency (Bazil et al. 2005)
- Acceptable safety and tolerability
  - Not metabolized in the liver
VAS Craving Scores: Alcohol Minus Water

Mason et al., Addict Biol, 2008
Effect of Gabapentin vs. Placebo on Pittsburgh Sleep Quality Index\textsuperscript{1}

\textsuperscript{1} Higher values indicate greater disturbance; subscale range 0-2

*** $p < 0.001$; ** $p < 0.05$; * $p < 0.06$

Mason et al., \textit{Addict Biol}, 2008
Summary of POC Human Lab Study of Gabapentin for Alcohol Dependence

Gabapentin 1200mg/d vs placebo was associated with
• Decreased craving (p < .05)
• Improved sleep (p < .05)
• Good safety and tolerability
• No evidence of abuse potential

A randomized controlled trial (RCT) to evaluate the efficacy of gabapentin for relapse prevention in alcohol dependence is warranted.

Mason et al., Addict Biol, 2008
Rates of Complete Abstinence and No Heavy Drinking on Study Over the 12-week Study in the ITT Population (N=150)

Mason et al., JAMA Intern Med, 2014
Gabapentin Effects on Symptoms of Protracted Abstinence
Over the 12-week Study in the ITT Population (N=150)

Beck Depression Inventory II
Linear dose effect p<0.001

Alcohol Craving Questionnaire
Linear dose effect p=0.019

Pittsburgh Sleep Quality Index
Linear dose effect p<0.02

Mason et al., JAMA Intern Med, 2014
Summary

• Gabapentin dose dependently, significantly improved
  - rates of complete abstinence and no heavy drinking
  - drinking quantity and frequency
  - GGT
  - alcohol craving
  - sleep disturbance
  - negative affective symptoms

• Gabapentin was well-tolerated with no serious or unexpected drug-related adverse events or evidence of abuse potential
Clinical Implications

- Gabapentin may offer a cost-effective treatment for AUD.

- Effect sizes for rates of abstinence and no heavy drinking were equivalent or superior to approved drugs, with unique benefits re: mood and sleep.

- Effects of gabapentin on drinking and symptoms of protracted abstinence lend support to the role of neuromodulating drugs that target brain stress systems to treat AUD.

- AUD is found – and gabapentin is widely used – across medical specialties. Reported benefits of gabapentin for AUD may result in a broader interest in AUD treatment across diverse medical settings.
Mifepristone
Rationale for Glucocorticoid Antagonism as a Treatment for Alcohol Dependence

• Heavy alcohol use and withdrawal dysregulate the balance between brain stress and reward systems
  - Abnormal HPA axis activity and glucocorticoid receptor feedback, and sensitization of CRF in the amygdala

• Mifepristone, a Type II glucocorticoid receptor antagonist, is available for re-purposing: FDA-approved to control hyperglycemia secondary to hypercortisolism in adults with endogenous Cushing’s syndrome who have type 2 diabetes mellitus or glucose intolerance (Korlym, Corcept Therapeutics)

• Clinically, administering mifepristone in alcoholics following acute withdrawal may normalize HPA axis dysregulation and thereby protect against relapse during protracted withdrawal
Alcohol-Cued Craving: Visual Analogue Scale (VAS) Scores

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<th>Strength</th>
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<th>Impulse</th>
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<tr>
<td>Placebo</td>
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<tr>
<td>Mifepristone</td>
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* p<0.05
Craving Response to Alcohol Cues and Subsequent Drinking: Mifepristone 600mg/d vs. Placebo (N = 50)

* $p < 0.05$

Summary of Mifepristone Results

• Mifepristone, relative to placebo, was associated with significantly less
  – Alcohol-induced craving in the lab
  – Alcohol consumption during 1-week of treatment and 1-week post treatment

• Mifepristone was well-tolerated
  – 52% reported no adverse events (AE’s)
  – All AE’s were of ≤ moderate severity
  – No serious or unexpected AE’s
  – No discontinuation due to AE’s
  – No evidence of abuse potential
  – Compliance by return pill count was high (mifepristone=100%, placebo=99%).
Discussion

• Reductions in craving, drinking and LFT’s relative to placebo suggest mifepristone has therapeutic potential for alcohol dependence.

• Mifepristone was well-tolerated, with no concerns re: safety, abuse potential, non-compliance or rebound following drug discontinuation.

• Positive outcomes for mifepristone
  – provide clinical validation of preclinical studies showing glucocorticoid antagonism reduces reinstatement of ethanol seeking and intake
  – lend support to the role of drugs that target abstinence-related dysregulation in brain stress systems for the treatment of alcohol dependence.

1-week of treatment with mifepristone to re-set the HPA-axis in protracted withdrawal, in conjunction with a course of psychosocial treatment, may offer a novel treatment paradigm that optimizes healthcare resources.
Tool Kit of Web-based Treatment Resources for Alcohol Use Disorder

Behavioral Therapies Used in Pharmacotherapy Trials

**AlcoholFree.today**
http://alcoholfree.today
• Patient and therapist materials from the U.S. multi-site acamprosate study

**COMBINE Monograph Series**
**Volume 2: Medical Management Treatment Manual**
• Treatment issues specific to pharmacotherapy trials in AUD

**Project MATCH Monograph Series**
https://pubs.niaaa.nih.gov/publications/projectmatch/matchintro.htm
• Motivational Enhancement Therapy (MET)
• Cognitive-Behavioral Coping Skills Therapy (CBT)
Tool Kit of Web-based Treatment Resources for Alcohol Use Disorder

Diagnosis and Treatment Information

https://pubs.niaaa.gov/publications/AssessingAlcohol/index.htm

NIAAA Navigator
https://alcoho1treatment.niaaa.nih.gov
• To identify local evidence-based AUD treatment options

The Surgeon General’s Report on Alcohol, Drugs and Health
Pharmacotherapy Guidance

The A.A. Member – Medications & Other Drugs
• Developed by physician members of A.A. to guide prescription use in AUD

American Psychiatric Association Practice Guidelines for the Pharmacological Treatment of Patients with Alcohol Use Disorder

Incorporating Alcohol Pharmacotherapies Into Medical Practice
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