One Step At a Time
–Treating Alcohol Dependence
ACMT Alcohol Abuse Academy 3/14/2013

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Disclosures

• Nothing to disclose

TM – alcohol, cocaine, opioids, struggling...

• “I can’t stop doing this. I woke up on my mom’s couch and had no idea what had happened. The last thing I remember was walking home from a meeting and I ran into my brother and (‘you know the one who has money, the crack problem’) and one thing led to another and I don’t know, I think I was hit by a car at one point…” (starts crying).
Alcohol Addiction

- Use to celebrate, compensate, or for any other reason, legitimate or not. Experience of the following:
  - Negative consequences
  - Limit setting & promises broken
  - Complaints are denied
  - Reliable symptoms of addictive disease become more evident
  - Continued use despite negative consequences
  - Loss of control, as in more use than planned (broken limits)
  - Unpredictability, as in use despite plan not to use
  - Compulsivity/preoccupation in thinking
  - Denial; Use of defenses to maintain denial
  - Build up of (or “break in”) tolerance
  - Remorse & guilt about use or behavior when using
  - Memory loss, mental confusion, irrational thinking
  - Family history of addictive behavior
  - Withdrawal discomfort (physical, mental, emotional, psychological).

Back to TM - symptoms of addiction

- Father died from alcoholism, one brother is in treatment/recovery and “he’s doing good.” Other brother has severe crack cocaine addiction.
- Frequent black outs.
- Violent/irrational. Assaulted room mate and has been in jail for assault. Usually doesn’t remember this.
- “I can’t drink at all. I get that first beer in me and I just can’t stop. I end up on my mom’s couch or somewhere else (‘like jail’) trying to remember what happened.

To Alcohol!

- The Cause of – and solution to – all of lives problems!
Alcohol Use and Disordered Drinking

"Attempts to change the course and consequences of heavy drinking undoubtedly started soon after the discovery that fermented grain or fruit yielded a drink that changed the way humans felt and behaved, because some of them behaved badly."


Spectrum of Drinking and Alcohol Use Disorders

Abstinence or low-risk drinking
At Risk Drinking
Harmful Drinking
Dependent Drinking
Chronic Dependence
Care Management

Risk Reduction
Risk Reduction

Health Promotion

Alcohol Use by Age: Use/Binge/Heavy

• Light Blue: Any Use
• Grey: Binge drinking: > 5 drinks in one setting
• Darker Blue: Heavy Use (> 5 drinks on more than 5 occasions during a 30 day period)
• Lifetime prevalence of alcohol use 88% in US
Treatment of persons with Alcohol Use Disorders

Other than custodial care professional treatment for Alcohol Use Disorders (AUDs) is a relatively recent addition, beginning with the promulgation of professional treatment programs in the latter part of the 20th century.

The Drunkards Progress…

Alcoholism (alcholismus chronicus)

These symptoms are formed in such a particular way that they form a disease group in themselves and thus merit being designated and described as a definite disease… It is this group of symptoms which I wish to designate by the name alcoholismus chronicus.”

-Magnus Huss in Chronic Alcoholism 1849
**Definition of Dependence DSM IV (1994)**

- The DSM says that addiction, or dependence, is present in an individual who demonstrates any combination of three or more of the following occurring at any time in the same 12-month period:
  - The development of tolerance to the chemical.
  - A characteristic withdrawal syndrome.
  - Use of the chemical to avoid or control withdrawal symptoms.
  - Repeated efforts to cut back or stop use.
  - Intoxication at inappropriate times (such as at work), or when withdrawal interferes with daily functioning (such as when hangover makes person too sick to go to work).
  - A reduction in social, occupational or recreational activities in favor of further substance use.
  - Continued substance use in spite of the individual having suffered social, emotional, or physical problems related to drug use.

**Lifetime Prevalence of Alcohol Dependence**

Table 1

<table>
<thead>
<tr>
<th>Birth Cohort</th>
<th>Age in years</th>
<th>N (%)</th>
<th>1980 Age in years</th>
<th>N (%)</th>
<th>N (1980) - N (1972)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1972-1975</td>
<td>18-27</td>
<td>6.8%</td>
<td>18-27</td>
<td>5.8%</td>
<td>-1%</td>
</tr>
<tr>
<td>1974-1976</td>
<td>18-27</td>
<td>6.0%</td>
<td>18-27</td>
<td>7.0%</td>
<td>+1%</td>
</tr>
<tr>
<td>1976-1978</td>
<td>18-27</td>
<td>6.9%</td>
<td>18-27</td>
<td>6.9%</td>
<td>-1%</td>
</tr>
<tr>
<td>Total (1972-1976)</td>
<td>18-27</td>
<td>22.8%</td>
<td>17.6% (0.3)</td>
<td>20-27</td>
<td>19.9% (3.4)</td>
</tr>
</tbody>
</table>

**Back to TM —which criteria does he meet?**

- Negative consequences?
  - Uses more than anticipated?
  - Preoccupation with substances?
  - Use to control withdrawal symptoms?
  - Tolerance?
  - Inappropriate intoxication (setting/pattern?)

- **What do I do…………….?**
  - Detox?
  - ED? (Mental Health or psychiatry assessment)
  - Inpatient? (yeah right, from clinic in a patient with Medicaid on a Friday afternoon)
  - Medications? (He’s on Suboxone™ for opioid dependence —only taking intermittently —about to be taken off.)
Treatment for Abuse and Dependence

• “At-risk” drinkers or those with ‘abuse’ only diagnosis who are identified and offered education and brief motivational counseling on average reduce their drinking by about 25% over the following year.”


Treatment Outcomes by Modality Similar

“Treatment outcome for dependence is remarkably similar across studies and treatment modalities, both behavioral and pharmacologic.”


1/3 rule = A third of individuals in a study will be fully abstinent or be in non-abstinent remissions by the end of a year, 30-40% will show substantial improvements but still have at least some episodes of heavy drinking and 20% to 30% will not show an effect.


What to target?

Drug Addiction is very different from drug dependence and withdrawal in terms of clinical symptoms.

Drug Addiction core clinical symptoms are craving and relapse to drug use.
Medication use in Alcohol Dependence

• Less than 1% of individuals meeting the criteria for diagnosis of alcohol dependence receive treatment with pharmacotherapies.

Pharmacology of Alcohol

Disulfiram (Antabuse™) Alcohol-sensitizing agent

• Discovered to cause ‘reaction’ after alcohol consumption during a study of use as treatment for parasitic infection (1948)
• Inhibits aldehyde dehydrogenase causing build-up of acetaldehyde (5-10x that of regular metabolism)
• Effectiveness limited by compliance
Disulfiram and the Disulfiram-Ethanol-Reaction (DER)

- Intensity varies depending upon both dose of ethanol and the dose of disulfiram.
- Most DERs are self-limited -30 minutes or less.
- Occasionally DER may be severe and cause severe cardiovascular abnormalities including hypotension, congestive heart failure, seizures and even death.
- Severe reactions typically caused by more than 500 mg/day of disulfiram and >2 ounces of ethanol; however, deaths have occurred with lower dose and with single drink.


The clinical use of disulfiram

“Disulfiram retains a place in standard alcoholism treatment programs because clinicians have found this agent useful for selected alcoholic patients. Clinical studies and clinical lore describe these patients as older, relapse-prone, socially stable, cognitively intact, not depressed, compulsive, capable of following rules, and tolerant of dependence. Another distinctly responsive (but evasive) group is court-probated patients.”


Disulfiram selection criteria and guidelines

- Proposed selection criteria: (1) patients who can tolerate a treatment relationship; (2) patients who are relapse-prone (but in treatment); (3) patients who have failed with less structured approaches; (4) patients in early abstinence who are in crisis or under severe stress; (5) patients in established recovery for whom individual or group psychotherapy is a relapse risk; and (6) patients who specifically request it.

- Prescriptions should be short-term and not allow automatic refills. It should be necessary to attend a treatment program in order to obtain them. Supervision and monitoring dramatically increase compliance.
Antabuse™ Availability

Disulfiram continued

- Additional mechanism of action involves inhibition of metabolism of catecholamines, in particular, dopamine. Dopamine levels subsequently increased. This mechanism thought to help attenuate ‘craving’.
- Currently being studied in the treatment of cocaine addiction, gambling addiction, other areas.

Acamprosate (Campral™) FDA approved 2004

- A GABA and homotaurine analogue that acts at N-methyl-D-aspartate (NMDA) and GABA-A channels.
- Dose-dependent effect.
- Not found to have significant abuse potential and without evidence of tolerance or withdrawal.
- Acamprosate reduces alcohol intake in animal models of alcohol dependence.
- 15/18 trials (5000 male and female outpatients with alcohol dependence (without illicit substance abuse) showed a positive effect vs placebo on abstinent outcomes (% of abstinent days over the study duration).
Acamprosate (Campral™) Effective? US trial

### OUTCOMES:

Acamprosate was associated with significantly higher percentage of abstinent days than placebo (52.3% for placebo, 58.2% for 2 grams, 62.7% for 3 grams (p = 0.01)).

- 741 screened
- 601 randomized
- 140 not randomized
- 98 not eligible
- 42 declined

<table>
<thead>
<tr>
<th>Group</th>
<th>% Abstinent days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>52.3%</td>
</tr>
<tr>
<td>Acamprosate 2g</td>
<td>58.2%</td>
</tr>
<tr>
<td>Acamprosate 3g</td>
<td>62.7%</td>
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### Effectiveness of acamprosate vs naltrexone

<table>
<thead>
<tr>
<th></th>
<th>Percentage attending program</th>
<th>Abstinence rates</th>
<th>Average number of days abstinence</th>
<th>Days until first breach of abstinence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acamprosate group</td>
<td>66.1%</td>
<td>50.8%</td>
<td>45.07 days</td>
<td>26.79 days</td>
</tr>
<tr>
<td>Naltrexone group</td>
<td>79.7%</td>
<td>66.1%</td>
<td>49.95 days</td>
<td>26.7 days</td>
</tr>
<tr>
<td>Drug combination group</td>
<td>83.1%</td>
<td>67.8%</td>
<td>53.58 days</td>
<td>37.32 days</td>
</tr>
</tbody>
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### Naltrexone (Vivitrol™ and Revia™)

µ-Opioid Receptor Knockout Mice Do Not Self-Administer Alcohol

Amanda J. Roberts, Jeffrey S. McDonald, Charles J. Heysen, Brigitte L. Kieffer, Hans W. D. Matthes, George F. Koob and Lisa H. Gold
Naltrexone continues

Naltrexone causes competitive antagonism to endogenous opioids (β-endorphins) which are released upon ingestion of ethanol; which removes the tonic inhibition by GABA interneurons (a disinhibition) on the dopaminergic neurons in the Ventral Tegmental Area (VTA) which terminate in the Nucleus Accumbens.

Opioids and alcohol—evidence of relation

Naltrexone effectively reduces the positive reinforcement associated with alcohol consumption by preventing/reducing dopamine release in the Nucleus Accumbens and hence reduces cravings for alcohol as well as the likelihood of a relapse to abusive drinking upon culmination of the treatment process.

Naltrexone (injectable/depot) as Vivitrol™

Naltrexone effectiveness linked to patients with family histories of alcoholism.

The varied susceptibility to beneficial effects of naltrexone has been suggested to be caused by single nucleotide polymorphisms in the OPRM1 gene which encodes for the μ-opioid receptor OPRM1 - 118G polymorphism carriers showing a better response to NTX over non-carriers.

Additional mechanism includes action at other opioid receptors i.e. delta agonism and modulation of the Hypothalamic-pituitary-adrenal
Additional treatments.... Prazosin?

- Prazosin, an alpha-1 adrenergic antagonist, may reduce central nervous system adrenergic activity and disrupt alcohol reinforcement and relapse.
- 24 persons with alcohol dependence randomized (mean age, 45 years; 79% male, 83% white) to prazosin (target dose, 4 mg in the morning and evening and 8 mg at bedtime) or placebo.
- Over the 6-week study period, participants attended 5 medical management sessions and carried a text pager that reminded them 3 times each day to take medications and once each day to call a telephone system for alcohol self-report.
- No difference between prazosin and placebo in change from baseline to 6 weeks for drinking days per week and mean drinks per week.
- Among the 20 participants who completed the study, those in the prazosin group reported fewer drinking days per week than the placebo group (3.2 days versus 5.6 days) over the last 3 weeks of the study, but there was no difference between groups in mean drinks per week.
- Among men who completed the study (n = 17), those in the prazosin group reported fewer drinking days per week (0.9 days versus 5.7 days) and mean drinks per week (2.6 drinks versus 20.8 drinks) than the placebo group over the last 3 weeks of the study.
- Craving and craving resistance did not differ between the 2 groups.

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Baclofen and general conclusions

CONCLUSIONS: Baclofen, a GABA(B) agonist, represents a possible new pharmaco-therapeutic approach to alcohol dependence. Despite encouraging preclinical data and positive clinical trials with baclofen to date, the current trial did not find evidence that baclofen is superior to placebo in the treatment of alcohol dependence. Additional clinical trials will be necessary to establish whether baclofen dosing does tell how baclofen efficacy in alcohol dependence and, if it does, what factors are pertinent to response.

Back to TM...

- He stayed in treatment. I kept him on buprenorphine for a period of time (until he was only intermittently taking it).
- Intensive Outpatient Groups (three 3 hour sessions).
- Counselor meetings 1-2 one hour sessions/week
- Anger management. Mental Health referral.
- Attempted to get him inpatient (1st discharged for ‘liaisons’ with female patient, 2nd left after an argument with a staff member at the treatment center). Halfway House referral pending.
• 1. We admitted we were powerless over alcohol - that our lives had become unmanageable.
• 2. Came to believe that a Power greater than ourselves could restore us to sanity.
• 3. Made a decision to turn our will and our lives over to the care of God as we understood Him.
• 4. Made a searching and fearless moral inventory of ourselves.
• 5. Admitted to God, to ourselves and to another human being the exact nature of our wrongs.
• 6. Were entirely ready to have God remove all these defects of character.
• 7. Humbly asked Him to remove our shortcomings.
• 8. Made a list of all persons we had harmed, and became willing to make amends to them all.
• 9. Made direct amends to such people whenever possible, except when to do so would injure them or others.
• 10. Continued to take personal inventory and when we were wrong promptly admitted it.
• 11. Sought through prayer and meditation to improve our conscious contact with God as we understood Him, praying only for knowledge of His will for us and the power to carry that out.
• 12. Having had a spiritual awakening as the result of these steps, we tried to carry this message to alcoholics and to practice these principles in all our affairs.

Thank You...

God grant me the Serenity

to accept the things
I cannot change

Courage to change the things I can

and the Wisdom

to know the difference