Medical Management of Substance Use Disorders: Does research translate to clinical practice

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Financial Disclosure Statement:
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• **Grants/Research:** National Institute of Drug Abuse, National Institute on Mental Health; Forest Laboratories; Envivo, Daiichi Sankyo, Sunovion

• **Consultant/Advisory Board /Speakers Bureau:** BDSI, Acadia, Otsuka, Generys, Radeas
Learning Objectives

• State evidence based pharmacological interventions for substance dependence.

• Identify major challenges associated with opioid, alcohol, marijuana & stimulant use treatment.

• Determine common treatment approaches for comorbid psychiatric disorders in substance-dependent patients.
Death Rates* for Three Selected Causes of Injury
North Carolina, 1968-2014

α - Transition from ICD-8 to ICD-9
β – Transition from ICD-9 to ICD-10

*Per 100,00, age-adjusted to the 2000 U.S. Standard Population
Source: Death files, 1968-2014, CDC WONDER
Analysis by Injury Epidemiology and Surveillance Unit
Heroin Deaths
North Carolina Residents, 2008-2015

884% increase from 2010 to 2015

565% increase from 2010 to 2014

Analysis by Injury Epidemiology and Surveillance Unit
Chronic Opioid Use Changes Brain Structure and Function

Potential physiologic mechanisms of tolerance and dependence include

- Changes in dopamine reward circuitry including decreased $D_2$ receptors (figure)$^1$
- Opioid receptor desensitization and downregulation$^2$
- Decreased synthesis of endogenous opioids$^2$
- Increased neuronal excitability when opioids are withdrawn$^2$

Behavioral/cognitive changes

- Craving induced by drug cues$^3$
- Loss of control over drug seeking behavior$^3$

<table>
<thead>
<tr>
<th>Medication</th>
<th>Target</th>
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</thead>
<tbody>
<tr>
<td><strong>FDA Approved</strong></td>
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</tr>
<tr>
<td>Methadone</td>
<td>Opioid agonist</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>Mu Opioid antagonist</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Mu partial agonist</td>
</tr>
<tr>
<td><strong>Under Investigation</strong></td>
<td></td>
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<tr>
<td>Modafinil</td>
<td>Glutamate enhancer</td>
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<tr>
<td>Tiagabine</td>
<td>GABA uptake inhibitor</td>
</tr>
<tr>
<td>Reserpine</td>
<td>Catecholamine depletor</td>
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<tr>
<td>cabergoline</td>
<td>D2 agonist</td>
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<tr>
<td>Vigabatrin</td>
<td>GABA transaminase</td>
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<tr>
<td>Antalarmin</td>
<td>CRF1 Receptor</td>
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<tr>
<td>Rimonabant</td>
<td>CB1 Receptor</td>
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### Medications for Treating Alcohol Dependence

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<tr>
<td><strong>FDA Approved</strong></td>
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<tr>
<td>Disulfiram</td>
<td>Aldehyde Dehydrogenase</td>
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<tr>
<td>Naltrexone</td>
<td>Mu Opioid Receptor</td>
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<tr>
<td>Inj Naltrexone</td>
<td>Glutamate Related</td>
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<tr>
<td>Acamprosate</td>
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<table>
<thead>
<tr>
<th><strong>Under Investigation</strong></th>
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<tr>
<td>Topiramate</td>
<td>GABA/Glutamate</td>
</tr>
<tr>
<td>Valproate</td>
<td>GABA/Glutamate</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>5 HT3 Receptor</td>
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<tr>
<td>Nalmefene</td>
<td>Mu Opioid Receptor</td>
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<tr>
<td>Baclofen</td>
<td>GABA$_B$ Receptor</td>
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*Slide courtesy: Dr T K Li, Director NIAAA*
Medications for Smoking

- Nicotine Replacement Therapies
- Sustained release Bupropion (Zyban®)
- Varenicline (Chantix®)
Intrinsic Activity: Full Agonist (Morphine), Partial Agonist (Buprenorphine), Antagonist (Naloxone)

Intrinsic Activity

Log Dose of Opioid

Full Agonist (Morphine)

Partial Agonist (Buprenorphine)

Antagonist (Naloxone)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine (Subutex®)</td>
<td>Opioid dependence</td>
<td>2mg and 8 mg SL</td>
</tr>
<tr>
<td>Buprenorphine + naloxone (Suboxone®)</td>
<td>Opioid dependence</td>
<td>2 mg/0.5 mg and 8 mg/2 mg SL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.7 mg/1.4 mg sl</td>
</tr>
<tr>
<td>Zubsolv®</td>
<td></td>
<td>4.2/0.7 mg buccal</td>
</tr>
<tr>
<td>Bunavail®</td>
<td></td>
<td>8-24 mg</td>
</tr>
<tr>
<td>Buprenorphine implant (Probufine)</td>
<td>Opioid dependence</td>
<td></td>
</tr>
</tbody>
</table>
Buprenorphine: evidence

- Is superior to clonidine and comparable to methadone for opiate withdrawal

- Is comparable to methadone for maintenance, retention may be better with high dose methadone.

- Methadone approved for pregnancy. New data suggest buprenorphine may be offer more benefits for neonate.

BMJ 2005;331:1352-1353
Short-Term Maintenance With Buprenorphine Is Associated With Relapse

Conclusions from a recent review

• Discontinuation of buprenorphine, even with gradual tapering, was associated with high rates of relapse to illicit opioids
  — Mean abstinence rate of 18% across studies

• Most patients relapsed within 1 month of buprenorphine discontinuation

Abstinence Rates After Buprenorphine Discontinuation

- Buprenorphine maintenance duration was 2 to 12 weeks followed by 1-11 week taper.
  Followed up 4 weeks to 6 months post buprenorphine cessation.

Drug Abuse Treatment Act (DATA) of 2000

- Allowed “Qualified” physicians to treat opioid dependence outside methadone facilities
  1. Addiction certification from approved organization, or
  2. Complete 8-hour course from approved organization
- DEA issues a new DEA number to use medication for opioid dependence
Who will be qualified to prescribe Buprenorphine? (continued)

• Maximum number of patients per physician is 30 for Year 1 and 100 thereafter. 275 for addiction certified physicians.

• Recently physician extenders have been approved to prescribe buprenorphine.
Naltrexone: evidence

- Oral effective dose 50-100 mg/day, blocks 90% of effects of 25 mg i.v. heroin
- Less effective than bup or methadone (Ahmadi et al, 2003)
- Poor compliance: < 5% at 9 months.
- Injectable naltrexone (Vivitrol®) is a 4 week extended release formulation to address compliance (Comer et al, 2006)

Methadone: summary of evidence

• Trend toward ↑ doses: In 1988, 80% received < 60 mg/day, in 2000, 35% took <60 mg/day.

• Higher doses (60-80 mg/day) more effective in blocking heroin effects.

• Methadone is a chronic potentially long term Rx

• Overdose. Methadone is a leading cause of unintentional single-drug poisonings

Medications for Stimulant dependence

- No approved medications for cocaine or methamphetamine dependence
- Modafinil, bupropion, Disulfiram & Topiramate, hold some promise.
- Cocaine vaccine under study

Medications for Cannabis Dependence

- No approved medications for cannabis
- Nabilone, lofexadine combined with dronabinol, gabapentin and N-acetylcysteine hold some promise.
- Cocaine vaccines have yielded inconsistent results

Martinez D, and Trifilieff P ASAM magazine April 13, 2015
Benzodiazepines in Alcohol Withdrawal

- BZ are first line agents.
- All BZ equally effective.
- **Longer acting BZ** may be more effective for withdrawal seizures & less rebound symptoms.
- **Shorter acting BZ** have less risk of oversedation but may have higher abuse potential.
- Consider risk benefit ratio for long term use in substance dependence

Holbrook et al CMAJ 160:649-55, 1999
FDA Approved Medications for Alcohol Dependence

• **Naltrexone**: reduces the rewarding and priming effects of alcohol.

• **Disulfiram**: produces aversive reaction by ↑ acetaldehyde accumulation.

• **Acamprosate**: maintains abstinence by improving persistent withdrawal symptoms.

Medication Combinations for Alcohol Dependence

• COMBINE study: compared combination of Medical Management (MM) with Naltrexone (NAL), acamprosate (ACAM), NAL + ACAM, placebo and combination of specialized counseling (CBI) with NAL, ACAM, NAL + ACAM, and PLAC

• 1383 subjects randomized for 16 weeks

• 1 year-follow up

COMBINE RESULTS

- MM + NAL > MM + PLA
- ACAM did not separate from placebo
- 6 to 7 patients need to be treated with MM + NAL or MM + CBI counseling or naltrexone for 1 additional patient to have a good clinical outcome. This "number needed to treat" is similar to depression, or type 2 diabetes.

Disulfiram for Alcohol Dependence

- Acetaldehyde dehydrogenase inhibitor
- Dose: 250-500 mg/day.
- Largest RCT failed to separate from placebo
- Little evidence of ↑ abstinence
- Tolerability issues. Black box warning.
- Effective if compliance enforced.

Fuller et al, JAMA 1986 256:1449-53
Anticonvulsants in Alcohol dependence

• Inhibit neuronal excitation at glutamate & GABA receptors & voltage gated ion channels
• Gabapentin and Topiramate have clinical supportive evidence
• Gabapentin commonly used during alcohol detoxification
• Topiramate is effective in reducing heavy drinking

<table>
<thead>
<tr>
<th>Disorder</th>
<th>OR</th>
</tr>
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<tbody>
<tr>
<td>Bipolar I disorder</td>
<td>7.9x</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>4.6x</td>
</tr>
<tr>
<td>Major depression</td>
<td>1.9</td>
</tr>
<tr>
<td>All bipolar disorders</td>
<td>4.7</td>
</tr>
</tbody>
</table>

Regier et al, ECA study 1990
SSRIs in Substance abuse and comorbid depression

- Minimal evidence of efficacy against core symptoms of substance dependence
- Efficacious in treating major depression, strongest effect if diagnosed after abstinence.

Pharmacotherapy For Alcohol and Comorbid Psychiatric Disorders

- Antidepressants and Lithium improve depressive and anxiety symptoms but no robust effect on drinking.
- One RCT positive for valproate in reducing drinking in comorbid bipolar disorder.
- Open label trials in schizophrenia suggest benefit for clozapine.

A Meta-Analysis of Smoking Cessation Pharmacotherapies: Majority Used 7-Day Point-Prevalence Abstinence Rates* (at ~6 Months)

<table>
<thead>
<tr>
<th>Cessation Pharmacotherapy</th>
<th>Number of Studies Included</th>
<th>Estimated Abstinence Rate (95%CI)</th>
<th>Estimated Odds Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine gum vs Placebo</td>
<td>13</td>
<td>23.7 (20.6, 26.7)</td>
<td>1.5 (1.3, 1.8)</td>
</tr>
<tr>
<td>Nicotine patch vs Placebo</td>
<td>27</td>
<td>17.7 (16.0, 19.5)</td>
<td>1.9 (1.7, 2.2)</td>
</tr>
<tr>
<td>Nicotine inhaler vs Placebo</td>
<td>4</td>
<td>22.8 (16.4, 29.2)</td>
<td>2.5 (1.7, 3.6)</td>
</tr>
<tr>
<td>Nicotine nasal spray vs Placebo</td>
<td>3</td>
<td>30.5 (21.8, 39.2)</td>
<td>2.7 (1.8, 4.1)</td>
</tr>
<tr>
<td>Bupropion SR vs Placebo</td>
<td>2</td>
<td>30.5 (23.2, 37.8)</td>
<td>2.1 (1.5, 3.0)</td>
</tr>
</tbody>
</table>

- Based on odds ratios, NRT and bupropion SR are twice as effective as placebo
- Estimated abstinence rates were predominantly based on 7-day point-prevalence data at 6 months

*A commonly used primary efficacy measure in past clinical trials
Chantix™ (varenicline) Phase 3 Studies: Efficacy Measurements: CO-Confirmed 4-Wk Continuous Abstinence Rates Wks 9–12

The 9-12 week Continuous Abstinence Rate is defined as the percentage of subjects who abstained from smoking (not even a puff) from Week 9 through 12 of the study as confirmed by both subject self-report and by end-expiratory carbon monoxide (CO) measurement.

The most frequently reported adverse events (>10%) with Chantix were nausea, headache, insomnia, and abnormal dreams.

Why do some feel that Rx does not work?

“I know someone who has been in and out of treatment a dozen times - it just doesn’t work!”

- Most Rx focused on a single episode of care. On average 3-4 Rx episodes are required for long term abstinence.
- Detoxification alone is not adequate Rx.
- Overall Rx approach should shift from acute intervention to long term management.
'Relapse' in selected disorders (O’Brien & McClellan (1996))

1-year relapse rates

- Addiction Rx
- ID Diabetes
- HTN
- Adult asthma
# Behavioral Therapies

<table>
<thead>
<tr>
<th>Treatment Intervention</th>
<th>Primary Target Population(s)</th>
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<tbody>
<tr>
<td></td>
<td>High-risk users</td>
</tr>
<tr>
<td>Brief intervention</td>
<td>✓</td>
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<tr>
<td>Motivational enhancement therapy</td>
<td></td>
</tr>
<tr>
<td>Cognitive behavioral therapy</td>
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<tr>
<td>Relapse prevention</td>
<td></td>
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<tr>
<td>Self Help</td>
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Slide courtesy: Dr T.K. Li, Director, NIAAA
Conclusions

• There are effective medications for substance abuse.

• Pharmacotherapy should be combined with behavioral interventions for optimal outcomes.

• Effective intervention should be long term.