Recent Advances in Pharmacotherapy for Substance Use Disorders (SUDs)

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Notes of Interest

- Dr. Teter has no real or potential conflicts of interest to report.
- Full references are available at the end of this presentation.
- The presentation was based in part on a recently-written SUD pharmacotherapy chapter:
  - Lecture focus: recent, newly confirmed, or under-utilized findings that can be applied at present.
  - Not an “in the pipeline” lecture.

Teter CJ 2012 (BCPP Review)
Learning Objectives

1. Discuss the efficacy of pharmacologic treatment options in the acute and long-term management of substance use disorders.

2. Describe treatment guidelines and clinical trials, including study design, strengths and weaknesses, and significance of findings for substance use disorders.

3. Discuss the role of drug therapy in the management of substance use disorders in special populations (e.g., pregnancy/lactation, high severity patients, etc.).

Definitions & Abbreviations

(…for purposes of this presentation)

- **AUD** = Alcohol Use Disorder
- **Etoh** = Ethanol (i.e., alcohol)
- **SUD** = Substance Use Disorder
  - Includes abuse and dependence
  - ETOH and other substances
- **WE** = Wernicke’s Encephalopathy
- **WKS** = Wernicke-Korsakoff Syndrome
AFFECTIVE
Major Depression
Bipolar Disorder

ANXIETY
Panic
GAD
OCD

PSYCHOTIC
Schizophrenia
Schizoaffective

Spectrum of SUDs

Patient Case
Case #1: Clinical Presentation

Chief Complaint:

- Patient is a 45-year-old white male with twenty year history of alcohol dependence who presents to the adult inpatient addiction unit following a relapse to heavy alcohol consumption.
- The patient’s wife brought him to the hospital for alcohol detoxification.
- It has been 3 hours since his last drink.

History of Present Illness (part #1):

- Patient thought he could handle a couple of drinks without serious consequences since he had been doing well.
  - Prior to this relapse, it had been at least 3.5 years since his last alcoholic beverage.
- Within hours of the first sip, he had consumed an entire 12-pack of beer.
- Since his drinking has escalated, his physical activity has decreased and his dietary intake is insufficient according to his wife.
Case #1: Clinical Presentation

History of Present Illness (part #2):

- The patient states that initially he wanted to have a beer or two “just to relax and enjoy the positive care-free feelings that only a beer can provide”.
- The patient endorsed drinking between a “6-pack to a 12-pack, depending on how tough the day had been” over the past 3 to 4 weeks.

Psychiatric History

- Patient has long-standing history of periodic bouts of depressive illness:
  - No history of medication management.
  - Alcohol appears to exacerbate depressive periods.
Case #1: Clinical Presentation

- **Past Medical History:**
  - Exercised-induced asthma

- **Allergies:**
  - NKDA

- **Social History:**
  - Tobacco (1 ppd); alcohol (+); illicit drugs (-)

- **Meds Prior to Admission:**
  - Albuterol inhaler prior to physical exertion

- **Family History:**
  - Father and brother (+) alcohol dependence

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Case #1: Clinical Presentation

- **Physical Examination:**
  - Blood pressure: 90/57 mmHg
  - Heart rate: 110 beats/min
  - Respiratory rate: 18 breaths/min
  - Temperature: 98 degrees F
  - Appearance:
    - Smell of alcohol on breath
    - Alert, well-groomed
    - Consistent dry, hacking cough
Case #1: Clinical Presentation

**Laboratory Values:**

- Na 146 mEq/L (135-147)
- K 4.8 mEq/L (3.5-5.0)
- Cl 103 mEq/L (95-105)
- HCO₃ 26 mEq/L (22-28)
- BUN 20 mg/dL (8-18)
- Scr 0.9 mg/dL (0.6-1.2)
- BG 65 mg/dL (70-110)
- CrCl 135 mL/min

- WBC 7200/mm³ (3200-9800)
- Hgb 15 mg/dL (14-18)
- Hct 45% (39-49)
- Bilirubin 0.9 mg/dL (0.1-1.0)
- Albumin 4 g/dL (4-6)
- ALT 20 U/L (0-35)
- AST 35 U/L (0-35)
- BAC 250 mg/dL (<80)

Case #1: Hospital Course

**Safety and stabilization:**

- Based on the patient’s presentation, he will be placed in a bed for observation while his BAC returns to zero and IV fluids are provided.
- After approximately 5 hours in observation the patient reports feeling “anxious” and beads of sweat are visible on his forehead.
Case #1: Hospital Course

- **Hospitalization <Day 1>:**
  - Patient is placed on CIWA-Ar checks for the next 24 hours and re-evaluated periodically.
  - Benzodiazepines will be dosed per CIWA-Ar scores and hospital protocol.
  - At this time, because the patient’s BG is low and his wife reports that he has not been eating well, the patient is given glucose via intravenous fluids.

Case #1: Hospital Course

- **Hospitalization <Day 2>:**
  - Patient becomes confused and develops a slow, ataxic gait.
  - All medications are held, but his condition does not improve.

**QUESTION:** Please identify potential treatment related problems that could have contributed to these symptoms in this particular patient.
Treatment-related Problem

- **Symptoms:**
  - Confusion and ataxic gait following the administration of glucose via IV administration.

- **Etiology:**
  - Patients with alcohol use disorders are often **thiamine deficient**.
  - Poor absorption and inadequate dietary intake.
  - Thiamine is a co-factor for normal glucose metabolism.
    - IV glucose may further and rapidly deplete thiamine reserves.

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Treatment-related Problem

- **Conclusion:**
  - Possible that administration of IV glucose, in a thiamine-deficient patient, caused or exacerbated encephalopathy.

- **[Questions for audience]:**
  - Which dose and route of thiamine do you recommend?
  - What evidence do you have for suggesting that particular thiamine regimen?
Pharmacotherapy Updates: Alcohol Use Disorders

Thiamine for Alcohol-related Wernicke-Korsakoff Syndrome (WKS)

- **APA Guidelines:**
  - Highly respected resource for information on treatment of psychiatric and substance use disorders.
  - Please see Essential Resources slide.
  - States the following:
    - "Consensus does suggest that thiamine be given routinely to all patients receiving treatment for a moderate to severe alcohol use disorder to treat or prevent common neurological sequelae of chronic alcohol use."

- **Guideline recommendations:**
  - Treatment for neurologic complications with "B complex vitamins (e.g., thiamine 50–100 mg/day i.m. or i.v.)".

*American Psychiatric Association Practice Guidelines (2006)*
Thiamine for Alcohol-related WKS (evidenced-based guidelines)

- **British Association of Psychopharmacology:**
  - States the following: “recommendations are based on uncontrolled trials and from empirical clinical practice”.
  - **Recommendations**:
    - Low risk individuals: minimum dose thiamine 300 mg/day orally during detoxification.
    - High risk individuals: thiamine 250 mg i.m. or i.v. once daily for 3–5 days.
    - Individuals with suspected/established WE: thiamine (i.m. or i.v.) > 500 mg should be given for 3–5 days.

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Thiamine for Alcohol-related WKS (meta-analysis)

- **Study objective**: evaluate the efficacy of thiamine in preventing and treating Wernicke-Korsakoff Syndrome (WKS) due to alcohol excess, including:
  - Thiamine dose
  - Thiamine route
  - Thiamine duration

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Lingford-Hughes et al 2004 (J Psychopharmacology)

Day et al 2008 (Cochrane Database Syst Rev)
Thiamine for Alcohol-related WKS (meta-analysis)

- Two studies (total of 177 participants) met inclusion criteria (one was unpublished):
  - However, one study too small (n=8) for quantitative analysis.
- Intervention:
  - Intramuscular thiamine (5, 20, 50, 100 and 200 mg) QD.
- Outcome:
  - Delayed alternation test (cognition).
  - Physical symptoms not assessed.

Day et al 2008 (Cochrane Database Syst Rev)

Thiamine for Alcohol-related WKS (meta-analysis)

- Thiamine 200 mg/day significantly superior to thiamine 5 mg/day on the number of trials taken to meet delayed alternation test criterion:
  - MD -17.90, 95% CI -35.4 to -0.4, P = 0.04.
  - Other doses non-significant as compared to 5 mg/day.
- Conclusion supplied by authors:
  - Insufficient evidence from randomized controlled clinical trials: thiamine dose, frequency, route, or duration.

Day et al 2008 (Cochrane Database Syst Rev)
There is a signal that higher thiamine doses than typically recommended (e.g., 100 mg) may be beneficial to our patients experiencing WKS.

Practical recommendations:
- Parental thiamine initially, followed by longer-term oral therapy for the following ‘at-risk’ patients:
  - Patients with active symptoms of Wernicke’s disease.
  - Patients who receive IV glucose solutions.
  - Patients at high risk for malnutrition.

Pharmacotherapy Updates: Opioid Use Disorders
Buprenorphine vs. Methadone (meta-analysis)

- **Objective:**
  - Meta-analysis review of randomized trials of buprenorphine maintenance versus placebo or methadone maintenance.

- **Study inclusion:**
  - Twenty-four studies (n=4,497 participants).

- **Pharmacotherapy intervention:**
  - Experimental: Buprenorphine
  - Controls: Placebo or Methadone

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Buprenorphine vs. Methadone (meta-analysis)

- Buprenorphine was associated with higher rates of retention in treatment at all doses evaluated (compared to placebo) and...
  - Medium and high buprenorphine doses suppressed heroin use greater than placebo.

- [Presenter note]: we know buprenorphine has demonstrated safety and efficacy from multiple studies:
  - However, may not be drug of choice for every patient.
**Buprenorphine vs. Methadone (meta-analysis)**

- **Flexible-dose buprenorphine** less effective compared to methadone in patient retention in treatment:
  - Eight flexible-dose studies.
  - Methadone superior at retaining patients in treatment as compared to buprenorphine:
    - Relative risk (RR) = 0.85 (95% CI 0.73 – 0.98).
  - Methadone (medium doses) superior to both low/medium dose buprenorphine for suppressing heroin use.

**Source:** Mattick et al 2008 (Cochrane Database Syst Rev)

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**Buprenorphine vs. Methadone (meta-analysis)**

- **Risk Ratio:**
  - $< 1.0 \rightarrow$ favors methadone
  - $> 1.0 \rightarrow$ favors buprenorphine
  - $RR = 0.85 \ (95\% \ CI \ 0.73 – 0.98)$

- **Additional notes:**
  - RR comparison: flexible dose
  - [buprenorphine vs. methadone]
  - Primary outcome: retention in treatment

**Source:** Mattick et al 2008 (Cochrane Database Syst Rev)
**Buprenorphine vs. Methadone (meta-analysis)**

- **SMD:**
  - \(<1.0\) \(\rightarrow\) favors buprenorphine
  - \(>1.0\) \(\rightarrow\) favors methadone
  - SMD = 0.27 (95% CI 0.05 – 0.5)

- **Additional notes:**
  - SMD comparison: fixed medium doses [buprenorphine vs. methadone]
  - Primary outcome: morphine [+]+ urines

**Summary:**

- Buprenorphine is an effective medication option for treating heroin dependence:
  - Offers many advantages (e.g., safety profile as compared to full opioid agonists).
  - However, according to this meta-analysis, it may be inferior to adequately dosed methadone for select treatment outcomes.

**Source:** Mattick et al 2008 (Cochrane Database Syst Rev)
Pharmacotherapy Updates: Nicotine Dependence

Nicotine Dependence Pharmacotherapy (meta-analysis; n=83 studies; 6-month data)

<table>
<thead>
<tr>
<th></th>
<th>Abstinence Rate (%)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong></td>
<td>13.8</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>NRTs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine gum (6-14 weeks)</td>
<td>19.0</td>
<td>1.5 (1.2-1.7)</td>
</tr>
<tr>
<td>Nicotine patch (6-14 weeks)</td>
<td>23.4</td>
<td>1.9 (1.7-2.2)</td>
</tr>
<tr>
<td>Nicotine gum (&gt; 14 weeks)</td>
<td>26.1</td>
<td>2.2 (1.5-3.2)</td>
</tr>
<tr>
<td>Nicotine patch (&gt; 14 weeks)</td>
<td>23.7</td>
<td>1.9 (1.7-2.3)</td>
</tr>
<tr>
<td><strong>Non-NRTs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion SR</td>
<td>24.2</td>
<td>2.0 (1.8-2.2)</td>
</tr>
<tr>
<td>Varenicline (1 mg/day)</td>
<td>25.4</td>
<td>2.1 (1.5-3.0)</td>
</tr>
<tr>
<td>Varenicline (2 mg/day)</td>
<td>33.2</td>
<td><strong>3.1</strong> <strong>(2.5-3.8)</strong></td>
</tr>
<tr>
<td><strong>Combination Strategies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patch (&gt; 14 weeks) + ad lib gum or spray</td>
<td>36.5</td>
<td><strong>3.6</strong> <strong>(2.5-5.2)</strong></td>
</tr>
<tr>
<td>Patch + bupropion SR</td>
<td>28.9</td>
<td>2.5 (1.9-3.4)</td>
</tr>
</tbody>
</table>

Nicotine Dependence Rx

- **Varenicline adverse events:**
  - FDA reporting on the possibility of *neuropsychiatric adverse events* among patients taking varenicline since 2007.
  - Initial report by the FDA described suicidal thoughts and aggressive/erratic behavior in patients taking varenicline.

- In 2009, FDA issued a *Public Health Advisory* describing changes in mood and behavior associated with varenicline (and bupropion).
  - **Symptoms:**
    - Hostility
    - Agitation
    - Depressed mood
    - Suicidality

**Source:** Food & Drug Administration Website (please see Reference list for more information)

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Nicotine Dependence Rx

- **Varenicline adverse events:**
  - FDA required *Boxed Warning* in the product labeling for these medications and patient medication guides were updated.
  - Ongoing review of *postmarketing adverse event reports*.

- FDA has also emphasized:
  - Efficacy of medications for treating tobacco dependence.
  - Multitude of benefits associated with smoking cessation.
  - Contribution of nicotine withdrawal to the presence of neuropsychiatric symptoms, however:
    - Some patients with adverse behavioral or mood events had continued to smoke.

**Food & Drug Administration Website (please see Reference list for more information)**
Nicotine Dependence Rx

- Nicotine replacement therapy (NRT):
  - Pregnancy category D
    - NRT for pregnant women made on a case-by-case basis.
    - Multiple issues to consider (e.g., which trimester of pregnancy).
  - According to the Clinical Practice Guidelines from the Department of Health and Human Services:
    - Pregnant smokers should be encouraged to quit smoking without the use of medication.
    - NRT may result in hemodynamic changes to mother and fetus.
    - Data lacking for non-NRT medications among pregnant smokers.

Source: Fiore et al. 2008 (Clinical Practice Guideline)

Pharmacotherapy Updates:
Stimulant Use Disorders
Stimulant Use Disorders Rx

- Concrete pharmacotherapy recommendations that can be located for the treatment of stimulant use disorders are scarce, including:
  - Intoxication, Withdrawal, Dependence

- Possible exceptions:
  - Management of cocaine-associated chest pain and myocardial infarction.
  - FDA-approved medications currently available with 'promise' for treating stimulant use disorders.

McCord et al 2008 (Circulation)

Stimulant Use Disorders Rx

- **American Heart Association guidelines:**
  - The acute use of beta-blockers may lead to worsening cocaine-related chest pain (due to coronary vasoconstriction) and hypertension due to unopposed alpha activity:
    - They are not recommended for acute use.
  - Recommended medication options:
    - Benzodiazepines
    - Aspirin
    - Nitroglycerin, nitroprusside
    - Phentolamine

McCord et al 2008 (Circulation)
Stimulant Use Disorders Rx

- APA Practice Guidelines specifically mention three medications as potential treatment options when combined with psychosocial approaches (after psychosocial approaches alone have failed):
  - **Topiramate**: biological target possibly GABA agonist effects.
  - **Disulfiram**: biological target possibly dopamine beta hydroxylase.
  - **Modafinil**: stimulant substitution; possibly dopamine or glutamate neurotransmission.

Essential Resources

- American Psychiatric Association (APA): www.psych.org
- American Society of Addiction Medicine (ASAM): http://www.asam.org/
- National Institute on Alcohol Abuse and Alcoholism (NIAAA): www.niaaa.nih.gov
- National Institute on Drug Abuse (NIDA): www.drugabuse.gov/
- Substance Abuse and Mental Health Services Administration (SAMHSA): www.samhsa.gov

TIPS from SAMHSA
- Public domain
- PDF format for free download (certain series)
- Wide variety of SUD topics covered:
  - Etoh Rx
  - Buprenorphine

Incorporating Alcohol Pharmacotherapies Into Medical Practice
A Treatment Improvement Protocol
TIP 49

Exhibit 6-4
AUD Medication Decision Grid

<table>
<thead>
<tr>
<th>Pretreatment Indicators</th>
<th>Acamprosate (Campral®)</th>
<th>Disulfiram (Antabuse®)</th>
<th>Oral Naltrexone (ReVia®, Depade®)</th>
<th>Injectable Naltrexone (Vivitrol®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal failure</td>
<td>X</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Significant liver disease</td>
<td>A</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>A</td>
<td>C</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Chronic pain</td>
<td>A</td>
<td>A</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Current opioid use</td>
<td>A</td>
<td>A</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Psychosis</td>
<td>A</td>
<td>C</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Unwilling or unable to sustain total abstinence</td>
<td>A</td>
<td>X</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Risk factors for poor medication adherence</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>A</td>
</tr>
<tr>
<td>Diabetes</td>
<td>A</td>
<td>C</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Obesity that precludes IM injection</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>X</td>
</tr>
<tr>
<td>Family history of AUDs</td>
<td>A</td>
<td>A</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bleeding/other coagulation disorders</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>C</td>
</tr>
<tr>
<td>High level of craving</td>
<td>A</td>
<td>A</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Opioid dependence in remission</td>
<td>A</td>
<td>A</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>History of postacute withdrawal syndrome</td>
<td>+</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>A</td>
<td>X</td>
<td>A</td>
<td>A</td>
</tr>
</tbody>
</table>

A = Appropriate to use
X = Contraindicated
C = Use with caution
+ = Particularly appropriate

Treatment Improvement Protocol Series #49 (2009)
**SUD Rx Progress**

- Pace is slower as compared to psychiatric disorders
- Many recommendations have not been adopted into common treatment discussions, despite being available for some time:
  - Higher doses of thiamine for alcohol-related WE
  - Higher doses of methadone for severe opioid dependence
    - Buprenorphine not always most advantageous
  - Varenicline may have high psychiatric risk profile
    - Despite highest likelihood for maintaining abstinence
  - NRT are pregnancy category D
    - Despite overall safety and tolerability profile
  - Beta-blockers may worsen cocaine-related chest pain
    - Benzodiazepines decrease CNS/physical arousal

**Patient Case (revisited)**

- Treatment-related problem:
  - Thiamine deficiency
  - Wernicke’s encephalopathy

- Questions for audience:
  - Which dose and route of thiamine do you recommend?
  - What evidence do you have for suggesting that particular thiamine regimen?
  - What have you seen in your clinical practice?


