The Role of Baclofen in Substance Dependence Treatment

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Objectives:

By the end of the presentation you should be able to:

1. Differentiate between substance abuse and substance dependence

2. Understand the theories behind baclofen’s proposed mechanism(s) of action in substance dependence treatment

3. Come to your own conclusion regarding use of baclofen in substance dependence treatment
KEY DEFINITIONS

Substance Abuse:\(^\text{1}\):  
- Maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12 month period:  
  1. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home  
  2. Recurrent substance use in situations in which it is physically hazardous  
  3. Recurrent substance-related legal problems  
  4. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance  
- Absence of dependence has been established

Substance Dependence\(^\text{1}\):  
- Maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12 month period:  
  1. Tolerance  
  2. Withdrawal  
  3. Substance is taken in larger amounts over a longer period than was intended  
  4. There is a persistent desire of unsuccessful efforts to cut down or control substance use  
  5. A great deal of time is spent in activities necessary to obtain, use, or recover from substance  
  6. Important social, occupational, or recreational activities are given up or reduced because of substance use  
  7. The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance  
- With or without physical dependence

ALCOHOL ABUSE/DEPENDENCE

EPIDEMIOLOGY:  
- According to the 2010 National Survey on Drug Use and Health, slightly more than half (51.8%) of Americans aged 12 or older reported being current drinkers of alcohol\(^\text{2}\)  
  o 23.1% participated in binge drinking (5 or more drinks on same occasion) at least once in the 30 days prior to survey  
  o 6.7% participated in heavy drinking (5 or more drinks on same occasion on at least five different days in the past month)  
- Approximately 4% of the global burden of disease can be attributed to alcohol consumption\(^\text{3}\)
### Genotypic, Phenotypic, and Environmental Factors that Increase Alcohol Dependence Risk

<table>
<thead>
<tr>
<th>Susceptibility Genes</th>
<th>Phenotype</th>
<th>Environment</th>
</tr>
</thead>
</table>
| Regions on chromosomes 1 and 4 that code for the following receptors:  
  - GABA<sub>A</sub>  
  - Serotonin 1b  
  - DRD4  
  - Tryptophan hydroxylase  
  - Neuropeptide Y  | Personality traits that include:  
  - Novelty seeking  
  - Impulsivity  
  - Aggression  
  - Depression  
  - Maximum number of alcoholic drinks consumed per day  | Religious background  
  - Urban residence (vs. rural)  
  - History of sexual abuse  
  - Being single  
  - Having deceased parents  |
| Genes that code for:  
  - ALDH2  
  - 5HTTLPR | |

ALDH2, aldehyde dehydrogenase 2; DRD4, type 4 dopamine receptor gene; GABA, γ-aminobutyric acid; 5HTTLPR, 5-hydroxytryptamine transporter

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### Pharmacologic Agents Used in the Treatment of Alcohol Dependence

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Range per Day</th>
<th>Indication</th>
<th>Monitoring</th>
<th>Duration of Dosing</th>
<th>Level of Evidence&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disulfiram&lt;sup&gt;b&lt;/sup&gt;</td>
<td>250 mg-500 mg</td>
<td>Deterrence</td>
<td>Facial flushing, Liver enzymes</td>
<td>Indefinite</td>
<td>B2</td>
</tr>
<tr>
<td>Acamprosate&lt;sup&gt;b&lt;/sup&gt;</td>
<td>999 mg-1,998 mg and higher</td>
<td>Craving</td>
<td>Patient reported craving, renal function</td>
<td>Indefinite</td>
<td>A1</td>
</tr>
<tr>
<td>Naltrexone&lt;sup&gt;b&lt;/sup&gt;</td>
<td>50 mg-100 mg</td>
<td>Craving</td>
<td>Patient reported craving</td>
<td>Indefinite</td>
<td>A1</td>
</tr>
<tr>
<td>Mood stabilizers (e.g. lamotrigine, topiramate, carbamazepine, valproic acid)</td>
<td>Seizure disorder doses</td>
<td>Craving</td>
<td>Patient reported craving, plasma drug levels</td>
<td>Indefinite</td>
<td>B2</td>
</tr>
<tr>
<td>Antidepressants (e.g. clomipramine, buproprion, doxepine, fluoxetine)</td>
<td>Depression doses</td>
<td>Craving, depression, anxiety</td>
<td>Patient reported craving</td>
<td>Indefinite</td>
<td>B2</td>
</tr>
</tbody>
</table>

<sup>a</sup>Strength of recommendations: A, B, C= good, moderate, and poor evidence, respectively. Quality of evidence: 1, evidence from more than 1 properly randomized, controlled trial. 2, evidence from more than 1 well-designed clinical trial with randomization, or dramatic results from uncontrolled experiments. 3, evidence from opinions of respected authorities, based on clinical experience, descriptive studies

<sup>b</sup>FDA approved medications

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**EFFICACY:**

- Meta-analysis found naltrexone to have a significant effect on maintenance of abstinence as well as prevention of heavy drinking<sup>5</sup>
  - Acamprosate shown only to support abstinence; did not influence alcohol consumption after first drink
    - When efficacy profiles of the two compared, acamprosate more effective in preventing a lapse; naltrexone better in preventing a lapse from becoming a relapse
- Acamprosate and naltrexone shown to be superior to non-pharmacologic therapy alone for maintenance of abstinence from alcohol
- Several studies have failed to prove disulfiram to be effective; poorly tolerated<sup>6</sup>
COCAINE ABUSE/DEPENDENCE

EPIDEMIOLOGY:

- According to the 2010 National Survey of Drug Use and Health, there were 637,000 persons aged 12 or older who had used cocaine for the first time within the past 12 months\(^2\)
  - \(~1,700\) initiates per day
  - Most (71.6%) of the recent initiated were 18 or older when first used
- Approximately 1.6 million people meet DSM-IV criteria for cocaine abuse or dependence\(^7\)

FDA APPROVED MEDICATIONS:

- None; treatment primarily behavioral\(^8\)
- Search for efficacious pharmacotherapies largely focused on dopaminergic agents
- No medication has demonstrated clear evidence of efficacy for the treatment of cocaine dependence\(^9\)

BACLOFEN

Pharmacologic Category\(^10\): Skeletal Muscle Relaxant (\(\gamma\)-aminobutyric acid (GABA\(_\alpha\)) agonist)

Labeled Indications\(^10\): Treatment of reversible spasticity associated with multiple sclerosis or spinal cord lesions

Mechanism of Action (for spasticity)\(^10\): Inhibits the transmission of both monosynaptic and polysynaptic reflexes at the spinal cord level, possibly by hyperpolarization of primary afferent fiber terminals, with resultant relief of muscle spasticity

Maximum Total Daily Dose\(^10\): 80 mg; doses up to 240 mg/day have been studied in multiple sclerosis patients

Hypothesized Mechanism of Action in Treating Substance Dependence:

- Several studies in rodents have demonstrated baclofen’s reducing effect on alcohol intake and motivation to consume alcohol\(^11\)-\(^13\)
- The cellular mechanism by which GABA\(_\alpha\) receptors exert their reducing effect on alcohol intake and motivation to consume alcohol yet to be defined\(^13\)
  - Experimental evidence suggest role for mesolimbic dopamine neurons\(^11\)-\(^13\)
    - Baclofen may inhibit alcohol stimulated dopamine release (through GABA)
  - Alcohol may increase GABA release from presynaptic nerve terminals\(^14\)
• GABA<sub>3</sub> agonists have been shown to modulate cocaine effects in several animal studies\textsuperscript{15-17}
• Human brain imaging studies indicate that baclofen may blunt the limbic activation that occurs to cocaine cues\textsuperscript{17}
  o Reduced limbic amygdala, orbitofrontal cortex, and anterior cingulated activity to visual cocaine cues
• GABA exerts inhibiting effect on tonic activity of dopamine neurons in the ventral tegmental area and in the nucleus accumbens\textsuperscript{11-17}
  o This may attenuate reinforcing effects of drug through modulation of dopamine transmission; the ventral tegmental area and nucleus accumbens are two structures involved in the reward system for all drugs

**Adverse Effects**\textsuperscript{10}:

• >10%:
  o Central Nervous System: Drowsiness, vertigo, psychiatric disturbances, insomnia, slurred speech, ataxia, hypotonia
  o Neuromuscular & Skeletal: Weakness
• 1% to 10%:
  o Cardiovascular: Hypotension
  o Central nervous system: Fatigue, confusion, headache
  o Dermatologic: Rash
  o Gastrointestinal: Nausea, constipation
  o Genitourinary: Polyuria
• <1%:
  o Palpitation, chest pain, syncope, euphoria, excitement, depression, hallucinations, xerostomia, anorexia, abnormal taste, abdominal pain, vomiting, diarrhea, enuresis, urinary retention, dysuria, impotence, inability to ejaculate, nocturia, paresthesia, hematuria, dyspnea

**Pharmacokinetics/Pharmacodynamics**\textsuperscript{10}:

• Onset of Action: 3-4 days
  o Peak effect: 5-10 days
• Absorption (dose dependent): Oral: Rapid
• Protein Binding: 30%
• Metabolism: Hepatic (15% of dose); 85% as unchanged drug
• Half-life Elimination: 3.5 hours
• Time to Peak, serum: Oral: Within 2-3 hours
• Excretion: Urine and feces
EFFECTIVENESS AND SAFETY OF BACLOFEN FOR MAINTENANCE OF ALCOHOL ABSTINENCE IN ALCOHOL-DEPENDENT PATIENTS WITH LIVER CIRRHOSIS: RANDOMIZED, DOUBLE-BLIND CONTROLLED STUDY

STUDY OBJECTIVE: To assess the effectiveness and safety of baclofen administration in achieving and maintaining alcohol abstinence in alcohol-dependent patients with liver cirrhosis

STUDY DESIGN: Randomized, double-blind placebo controlled study

STUDY SUBJECTS: Between October 2003 and November 2006, all alcoholic dependent patients affected by liver cirrhosis consecutively referred to Institute of Internal Medicine of the Catholic University in Rome, Italy

- **Inclusion Criteria:** Ages 18 to 75 years, diagnosis of alcohol dependence according to DSM-IV criteria, diagnosis of liver cirrhosis, and alcohol intake of at least two heavy drinking days per week on average, and an average overall consumption of 21 drinks per week or more for men and 14 drinks per week or more for women during the 4 weeks prior to enrollment, and a presence of a referred family member able to assist with drug administration and monitoring

- **Exclusion Criteria:** Severe heart or lung diseases, abnormal renal function, hepatorenal syndrome, malignant disease, metabolic disease, hepatic encephalopathy, treatment with interferon or corticosteroids within the past 60 days, psychopathological illness treated with psychoactive drugs, epilepsy, and addiction to drugs other than nicotine

PRIMARY OUTCOME: Proportion of patients achieving and maintaining alcohol abstinence (total abstinence from alcohol and cumulative abstinence duration)

SECONDARY OUTCOME(S): Difference in craving measures between groups (Obsessive Compulsive Drinking Scale (OCDS))

METHODS:

- Patients admitted to hospital for 3-4 days
- Randomly allocated to either oral baclofen or placebo
- Treatment was given for 12 consecutive weeks
  - First 3 days baclofen 5 mg TID; subsequently increased to 10 mg TID
- Graded clinical condition at time of enrollment according to Child-Pugh classifications
- Assessed all patients as outpatients every week for the first month and then every 2 weeks
  - Review of drinking, overall functioning, difficulties with treatment adherence, and adverse effects assessed
  - Pill counts to assess treatment adherence
  - Routine psychological support counseling at every visit
- Assessed abstinence from alcohol at every visit on basis of patient’s self-evaluation and family member interview
  - Highest estimates used if reports conflicted
  - Measured alcohol content of blood, urine, or both to confirm alcohol consumption

Mehvar 5
- Alcohol relapse defined as a daily alcohol intake of more than four drinks or an overall consumption of 14 drinks or more per week during at least four weeks
- Alcohol lapse defined as any episode of alcohol consumption not classified as relapse
- Recorded the presence of possible side-effects attributable to drug withdrawal every week for the first 4 weeks after drug discontinuation
- Craving level assessed at start of study and at every visit using OCDS
- Measured liver enzymes and biological markers of alcohol abuse, ammonia, creatinine at T0, T4, T6, T8, T10, T12
  - Albumin measured T0, T4, T8, and T12

**STATISTICAL ANALYSES:**
- A priori sample size calculation: At least 40 patients in each group (power 0.8)
- All patients who terminated treatment before end of study considered relapses
  - Cumulative abstinence duration calculated with data available at time of last visit
- Analysis done by intention to treat

**RESULTS:**
- 148 alcohol-dependent patients initially screened
  - 64 excluded
  - 84 randomly allocated either placebo or baclofen

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=42)</th>
<th>Baclofen (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>49.5 (44.0-60.0)</td>
<td>49.0 (43.0-61.0)</td>
</tr>
<tr>
<td>Men</td>
<td>29 (69%)</td>
<td>32 (76%)</td>
</tr>
<tr>
<td>Married</td>
<td>24 (57%)</td>
<td>27 (64%)</td>
</tr>
<tr>
<td>Education &gt;13 years</td>
<td>9 (21%)</td>
<td>12 (29%)</td>
</tr>
<tr>
<td>Employed</td>
<td>31 (74%)</td>
<td>33 (79%)</td>
</tr>
<tr>
<td><strong>Addiction Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of daily consumption of alcohol (years)</td>
<td>16.0 (13.0-23.0)</td>
<td>16.0 (12.0-24.0)</td>
</tr>
<tr>
<td>Duration of alcohol abuse (years)</td>
<td>22.0 (17.0-26.0)</td>
<td>22.0 (17.0-27.0)</td>
</tr>
<tr>
<td>Obsessive Compulsive Drinking Scale (OCDS) scores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCDS Total</td>
<td>25.0 (22.0-29.0)</td>
<td>28.0 (23.0-32.0)</td>
</tr>
<tr>
<td>Compulsive Subscale</td>
<td>9.5 (8.0-12.0)</td>
<td>12.0 (9.0-14.0)</td>
</tr>
<tr>
<td>Obsessive Subscale</td>
<td>15.0 (14.0-18.0)</td>
<td>16.5 (14.0-20.0)</td>
</tr>
<tr>
<td>Alcohol withdrawal syndrome treated by diazepam</td>
<td>11 (26%)</td>
<td>13 (31%)</td>
</tr>
<tr>
<td><strong>Liver Cirrhosis Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child-Pugh Score</td>
<td>9.0 (8.0-11.0)</td>
<td>9.0 (8.0-11.0)</td>
</tr>
<tr>
<td>Child-Pugh Class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>6 (14%)</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>B</td>
<td>20 (48%)</td>
<td>20 (48%)</td>
</tr>
<tr>
<td>C</td>
<td>16 (38%)</td>
<td>18 (43%)</td>
</tr>
<tr>
<td>Hepatitis B virus positive</td>
<td>10 (24%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Hepatitis C virus positive</td>
<td>12 (29%)</td>
<td>12 (29%)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>Baclofen</td>
</tr>
<tr>
<td>--------------------------</td>
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</tr>
<tr>
<td>Total Alcohol Abstinence (n [%])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child-Pugh A</td>
<td>1/6 (17)</td>
<td>3/4 (75)</td>
</tr>
<tr>
<td>Child-Pugh B</td>
<td>5/20 (25)</td>
<td>12/20 (60)</td>
</tr>
<tr>
<td>Child-Pugh C</td>
<td>6/16 (38)</td>
<td>15/18 (83)</td>
</tr>
<tr>
<td>Total</td>
<td>12/42 (29)</td>
<td>30/42 (71)</td>
</tr>
</tbody>
</table>

- No significant difference in number of dropouts (6/42 baclofen vs. 13/42 placebo; p=0.12)
- Cumulative abstinence duration about two-fold higher in patients allocated baclofen than those assigned placebo (mean 62.8 vs. 30.8 days; p=0.001)
- Survival analysis indicated a significantly greater chance of remaining free of lapse and relapse to alcohol consumption in individuals allocated baclofen
  - At 30 days of randomization, 6 patients (14%) in baclofen group had relapsed compared with 16 patients (38%) in placebo group
  - At 60 days of randomization, 8 patients (19%) in baclofen group had relapsed compared with 19 patients (45%) in placebo group
- Baclofen significantly reduced craving scores (p=0.0004)
  - Obsessive subscale p=0.0012
  - Compulsive subscale p=0.0002
- Patients allocated baclofen had significantly reduced alanine aminotransferase, bilirubin, international normalized ratio, and γ glutamyltransferase from baseline and significantly increased albumin
- No patients discontinued treatment because of a side effect
- No patients reported euphoria or other pleasant effects or craving for baclofen
- Treatment adherence did not differ between groups

**AUTHOR’S CONCLUSION:** “Our results show that oral administration of baclofen is significantly more effective than placebo at achieving and maintaining alcohol abstinence and at increasing cumulative abstinence duration in alcohol-dependent patients with liver cirrhosis. This reduction in self-reported alcohol use is associated with significant reductions in clinical markers of liver injury...”

**REVIEWER’S OPINION**

<table>
<thead>
<tr>
<th>STRENGTHS</th>
<th>WEAKNESSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Included patients with liver disease</td>
<td>Small sample size</td>
</tr>
<tr>
<td>Monitored lab values (liver, renal)</td>
<td>Did not meet power after dropouts</td>
</tr>
<tr>
<td>Self-report/Family report of alcohol intake</td>
<td>Not generalizable</td>
</tr>
<tr>
<td>Psychological support involved</td>
<td></td>
</tr>
<tr>
<td>Self-report/Family report of alcohol intake</td>
<td></td>
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</tbody>
</table>
EFFICACY AND SAFETY OF BACLOFEN FOR ALCOHOL DEPENDENCE: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

STUDY OBJECTIVE: To explore the efficacy and tolerability of baclofen in alcohol dependence

STUDY DESIGN: Randomized, double-blind, placebo-controlled

STUDY SUBJECTS:
- **Inclusion Criteria:** Ages between 18 and 60 years old, DSM-IV criteria for current alcohol dependence, at least 2 heavy drinking days per week on average during the 4 weeks prior to screening, ability to refrain from alcohol for 3 days prior to randomization visit
- **Exclusion Criteria:** Clinically significant medical disease that might interfere with evaluation of study medication of presence of a safety concern, clinically significant psychiatric illness, suicidal ideation, concurrent use of any psychotropic medications including antidepressants, mood stabilizers, antipsychotics, anxiolytics, stimulants, or hypnotics with the exception that stable doses of antidepressants for 2 months prior to screening was permitted, aspartate aminotransferase (AST), alanine transaminase (ALT), or γ-glutamyl transferase (GGT) level >3 times the upper limit of normal (ULN), bilirubin >ULN, or serum creatinine >ULN

PRIMARY OUTCOME: The percent of heavy drinking days, the percent of abstinence

METHODS:
- Patients recruited through newspaper and radio advertisements in Raleigh, Durham, and Chapel Hill, North Carolina area
- Randomization implemented stratifying on gender
- 44 men and 36 women randomized
  - 22 men received baclofen, 22 men received placebo
  - 18 women received baclofen, 18 women received placebo
- At intake patients completed the 90 day pretreatment Timeline Followback interview (TLFB), Alcohol Dependence Scale, Zung Self-Rating Depression Scale, Spielberger Trait and State Anxiety Inventory (STAI), and the Penn Alcohol Craving Scale (PACS)
- Patients received 8 BRENDA therapy sessions (one at each visit)
- At week 0, patients were provided a 1-week blister pack of baclofen or placebo with written instructions to titrate dosage
  - Final baclofen dose: 30 mg/day
- Patients also supplied with calendar style diary to track pill taking, drinking, and any side effects
- Patients medically monitored on a weekly (for the first month) and biweekly (for the 2nd and 3rd month) basis
  - Vital signs, concomitant medications, in depth side effect monitoring using adverse events form
  - Week 4, blood was drawn for evaluation of liver function
- At each visit patients given breathalyzer test (Blood Alcohol Content (BAC) had to be ≤0.02 g/dL), TLFB interview, Zung, STAI, and PACS

STATISTICAL ANALYSES:
- Intent to treat analysis
- Used generalized estimating equations (GEE) approach
RESULTS:
- Included 80 patients (40 baclofen, 40 placebo)
  - Demographically similar (no statistically significant differences)
- 32/40 (placebo) patients completed study vs. 28/40 (baclofen) patients (p=0.44)

- Significant time effect was found (p<0.001) but no significant baclofen effect detected (p=0.56) for percent heavy drinking days during treatment
  - 25.5%(±23.6%) for placebo
  - 25.9% (±23.3%) for baclofen
  - Incorporating repeated measures through GEE analysis indicated a non-significant difference between placebo and baclofen (p=0.73)
Marginal effect for time was found (p=0.07) but no significant baclofen effect was detected (p=0.50) for percent abstinent days during treatment
  - 50.6%(±25.9%) for placebo
  - 49.9%(±27.9%) for baclofen
- No significant differences between placebo and baclofen patients for craving (p=0.13)
- No significant differences between placebo and baclofen patients for depression (p=0.10) or trait anxiety (p=0.14)
  - Significant difference in on-average severity (p=0.02)
    - Possible baclofen effect on reducing anxiety levels
- No difference between placebo and baclofen for time to first usage (p=0.13)
- No difference between placebo and baclofen for time to first heavy usage or relapse (p=0.76)
- Marginal difference between placebo and baclofen for time to 2 consecutive abstinences (p=0.07)
- No difference between placebo and baclofen for time to 2 consecutive heavy usages (p=0.55)
- No evidence of treatment differences acting differentially dependent on gender for percent heavy drinking days and percent abstinent days (p=0.91 and p=0.36, respectively)
  - Non-significant interactive effect for gender for all time to analyses
- Neither high baseline levels of craving for alcohol or levels of anxiety associated with response to baclofen
- Medication compliance comparable between baclofen and placebo groups (p>0.28)
  - 71.6%-96.4% placebo; 47.8-94.9% baclofen
- Only 2 adverse events affected more than 5% of the sample
  - Drowsiness (10% placebo, 28% baclofen)
  - Headaches (10% placebo, 3% baclofen)

**AUTHOR’S CONCLUSION:** “...Current trial did not find evidence that baclofen at a dose of 10 mg three times per day was superior to placebo in the treatment of alcohol dependence. No baclofen effect was found on heavy drinking or abstinent days. The presence of high levels of anxiety or high craving was not associated with a baclofen response although there was some evidence that baclofen has anxiolytic effects.”

**REVIEWER’S OPINION**

<table>
<thead>
<tr>
<th>STRENGTHS</th>
<th>WEAKNESSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized, double-blind, placebo controlled</td>
<td>Small sample size, many dropouts</td>
</tr>
<tr>
<td>Used dose that was found effective in previous trials</td>
<td>Psychological support involved</td>
</tr>
<tr>
<td>Evaluation by gender</td>
<td>No referred family member</td>
</tr>
<tr>
<td>Time to events outcomes</td>
<td>Patients recruited through advertisement</td>
</tr>
</tbody>
</table>
CLINICAL EXPERIENCE WITH BACLOFEN IN THE MANAGEMENT OF ALCOHOL-DEPENDENT PATIENTS WITH A PSYCHIATRIC COMORBIDITY: A SELECTED CASE SERIES

STUDY SUBJECTS:

- **Inclusion Criteria:** Prior unsuccessful treatment with and/or contraindications to standard alcohol pharmacotherapy, had received a range of other alcohol treatment modalities, were on concurrent psychotropic medication, available for clinic follow up and provided informed consent for treatment with baclofen
- **Exclusion Criteria:** No previous treatment with alcohol pharmacotherapy, inaccessible for follow up, pregnancy, history of epilepsy

METHODS:

- All patients required admission to a 15-bed inpatient withdrawal unit
- Baclofen initiated once the patient had undergone alcohol withdrawal
- Baclofen prescribed at 5 mg TID for 3 days, then 10 mg TID as the usual maintenance dose
  - Final stabilization dose prescribed at discretion of treating clinician
- Adverse reactions recorded, including reasons for discontinuation of treatment
- All patients offered individual counseling and medical review
- Patients provided with detailed information about baclofen (risk/benefits, studies in alcohol dependence)
- Demographic and clinic data collected

RESULTS:

- 541 admissions to the unit in 2009
  - 126 had comorbid psychotic mental illness
    - Only 21 met criteria
      - 8 of the 21 patients lost to clinic follow up
- Mean age of 49 years (range 41-62 years)
- 10 males, 3 females
- Mean duration of alcohol dependence 15 years (range 2-32 years)
- Baseline daily alcohol consumption ranged from 110 to 400 g daily
- 13 patients had a depressive disorder and 8 of those also had a co-existing anxiety disorder
- 9 patients reported significant suicidal ideation prior to treatment
- Follow up periods ranged from 4 days to 27 months
  - 2 patients immediately relapsed after discharge (both non-compliant with baclofen)
- Baclofen doses prescribed ranged from 30 mg to 275 mg daily, administered in three divided doses
- Most common side effects were tiredness and sedation
  - One patient developed severe back pain at doses of 120 mg and above
  - One patient developed occasional bedwetting and dizziness at 275 mg
  - Two patients experienced an overdose of other CNS depressants in combination with baclofen in the first week of treatment, both requiring emergency review
<table>
<thead>
<tr>
<th></th>
<th>Age,sex</th>
<th>Baseline daily alcohol</th>
<th>Duration dependence</th>
<th>Concurrent problems</th>
<th>Comorbid diagnoses</th>
<th>Other psychotropics</th>
<th>Length of follow up</th>
<th>Total drinking days; amount per day (grams)</th>
<th>Daily baclofen dose</th>
<th>Baclofen side effects</th>
<th>Reported effect on alcohol cravings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47, F</td>
<td>320 g</td>
<td>7 years</td>
<td>HTN</td>
<td>Depression</td>
<td>Fluoxetine 20 mg</td>
<td>18 months</td>
<td>0 days</td>
<td>50-70 mg</td>
<td>Drowsy unless taken with food</td>
<td>Total suppression of cravings</td>
</tr>
<tr>
<td>2</td>
<td>44, M</td>
<td>150-300 g</td>
<td>16 years</td>
<td>Homeless</td>
<td>Depression, Panic disorder</td>
<td>Mianserin 100 mg, Alprazolam 2 mg TID</td>
<td>16 months</td>
<td>0 days</td>
<td>0-75 mg daily</td>
<td>275 mg daily: somnolence, dizziness, bedwetting</td>
<td>275 mg: total suppression of cravings</td>
</tr>
<tr>
<td>3</td>
<td>43, M</td>
<td>110 g</td>
<td>9 years</td>
<td>Suicidal ideation, Unemployed</td>
<td>Panic disorder</td>
<td>Paroxetine 40 mg</td>
<td>29 weeks</td>
<td>0 days for 23 weeks. Relapse from week 24</td>
<td>0 days</td>
<td>30 mg</td>
<td>Forgetful</td>
</tr>
<tr>
<td>4</td>
<td>62, M</td>
<td>150 g</td>
<td>30 years</td>
<td>Gastric ulcer, Anemia, Unemployed, Suicidal ideation</td>
<td>Social phobia, Depression, GAD, Codeine misuse</td>
<td>Escitalopram 40 mg</td>
<td>15 weeks</td>
<td>0 days</td>
<td>30 mg</td>
<td>Reduced anxiety. Mild headache, tiredness</td>
<td>Not stated</td>
</tr>
<tr>
<td>5</td>
<td>51, M</td>
<td>180-240 g</td>
<td>9 years</td>
<td>Suicidal ideation, Unemployment</td>
<td>THC dependence, Depression, PTSD, Hepatitis C</td>
<td>Paroxetine 20 mg, Naltrexone 50 mg</td>
<td>7 weeks</td>
<td>0 days</td>
<td>10-30 mg</td>
<td>None reported</td>
<td>Not stated</td>
</tr>
<tr>
<td>6</td>
<td>47, M</td>
<td>200-300 g</td>
<td>12 years</td>
<td>Suicidal ideation, Drink driving charge, Gastritis</td>
<td>Depression</td>
<td>Citalopram 20 mg</td>
<td>23 weeks</td>
<td>6 days: 30-120 g</td>
<td>30-60 mg</td>
<td>Reduced anxiety</td>
<td>Reduced cravings; greater effect at 60 mg</td>
</tr>
<tr>
<td>7</td>
<td>55, M</td>
<td>120 g</td>
<td>32 years</td>
<td>Unemployment, Suicide attempt</td>
<td>Depression, Opioid Dependence, Hepatitis C, THC dependence</td>
<td>Mirtazapine 60-90 mg, Buprenorphine 4 mg</td>
<td>27 months</td>
<td>First 12 months: 9 drinking days (45-150 g), Second 15 months: 0 days</td>
<td>30 mg</td>
<td>Transient sedation, dizziness, ’speed like’ effect at initiation</td>
<td>Total suppression of cravings</td>
</tr>
<tr>
<td>8</td>
<td>57, M</td>
<td>300 g</td>
<td>32 years</td>
<td>Suicidal ideation, Repeated ED visits, Divorced, Homeless</td>
<td>Depression, Gambling</td>
<td>Desvenlafaxine 50-100 mg</td>
<td>20 weeks</td>
<td>140 days: 30-40 g</td>
<td>100-150 mg</td>
<td>&gt;120 mg severe back pain; resolved on cessation</td>
<td>Marked reduction in cravings</td>
</tr>
</tbody>
</table>

Mehvar 12
<table>
<thead>
<tr>
<th></th>
<th>Age,sex</th>
<th>Baseline daily alcohol</th>
<th>Duration dependence</th>
<th>Concurrent problems</th>
<th>Comorbid diagnoses</th>
<th>Other psychotropics</th>
<th>Length of follow up</th>
<th>Total drinking days; amount per day (grams)</th>
<th>Daily baclofen dose</th>
<th>Baclofen side effects</th>
<th>Reported effect on alcohol cravings</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>41, M</td>
<td>300-400 g</td>
<td>2 years</td>
<td>Depression, Anxiety</td>
<td>Sertraline 50 mg</td>
<td>14 days</td>
<td>Lapse at day 14; 20 g</td>
<td>30 mg</td>
<td>Transient tiredness, improved sleep and anxiety</td>
<td>Reduced cravings</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>47, F</td>
<td>150-200 g</td>
<td>12 years</td>
<td>Depression</td>
<td>Citalopram 60 mg</td>
<td>7 days</td>
<td>Relapsed day after discharge</td>
<td>30 mg</td>
<td>Never took baclofen</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>50, F</td>
<td>150-200 g</td>
<td>20 years</td>
<td>Suicidal ideation, Multiple ED visits, Withdrawal seizures</td>
<td>Panic Disorder, Depression, Anxiety</td>
<td>Olanzapine 5 mg, Fluoxetine 20 mg</td>
<td>7 days</td>
<td>Relapsed day after discharge</td>
<td>30 mg</td>
<td>Never took baclofen</td>
<td>None</td>
</tr>
<tr>
<td>12</td>
<td>47, M</td>
<td>240 g</td>
<td>7 years</td>
<td>Multiple past suicide attempts, Unemployed</td>
<td>Borderline, Antisocial Personality Disorder, Depression, Opioid dependence, Hepatitis C</td>
<td>Venlafaxine XR 225 mg, Buprenorphine 32 mg</td>
<td>2 months</td>
<td>0 days for 2 months</td>
<td>30 mg</td>
<td>Acute anxiolytic effect: rapid unapproved dose escalation, polypharmacy overdose</td>
<td>Reduced cravings</td>
</tr>
<tr>
<td>13</td>
<td>47, M</td>
<td>200-400 g</td>
<td>8 years</td>
<td>Accidental overdoses, Suicidal ideation</td>
<td>Depression, GAD, Social Phobia</td>
<td>Venlafaxine 150 mg</td>
<td>4 days</td>
<td>4 days: amount unknown</td>
<td>30 mg</td>
<td>Polyparmacy overdose</td>
<td>None</td>
</tr>
</tbody>
</table>

**AUTHOR'S CONCLUSION:** “In our opinion, baclofen is not a first-line treatment for relapse prevention in alcohol dependence in patients with psychiatric comorbidity. However, baclofen could be considered when first-line agents are ineffective, poorly tolerated, or contraindicated.”

**REVIEWER'S OPINION:**

<table>
<thead>
<tr>
<th>STRENGTHS</th>
<th>WEAKNESSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Included comorbid psychiatric disorders, included patients on other psychotropics</td>
<td>Case series, retrospective audit of clinical data</td>
</tr>
<tr>
<td>Included patients with comorbid substance abuse disorders</td>
<td>Did not exclude patients on other medications for substance abuse(naltrexone, buprenorphine)</td>
</tr>
<tr>
<td>Titrated baclofen dose to effective dose per patient</td>
<td>2 patients overdosed in combination with other medications</td>
</tr>
</tbody>
</table>
RANDOMIZED PLACEBO-CONTROLLED TRIAL OF BACLOFEN FOR COCAINE DEPENDENCE: PRELIMINARY EFFECTS FOR INDIVIDUALS WITH CHRONIC PATTERNS OF COCAINE USE

STUDY OBJECTIVE: To determine whether baclofen produced effects significant enough to warrant a full-scale efficacy trial

STUDY DESIGN: 2 group, randomized, placebo-controlled, double-blind trial conducted from October 1997 to May 1999

STUDY SUBJECTS:
- **Inclusion Criteria:** Cocaine dependence diagnosed using DSM-IV criteria, aged 18 to 65 years, English literacy, understand risks/benefits to participation, provide voluntary informed consent
- **Exclusion Criteria:** Dependence on alcohol or other substances, current psychiatric disorder requiring treatment, active medical conditions that interfere with participation, history of seizures, unstable behavior during screening period, asthma requiring treatment

OUTCOMES: Urine drug testing results for cocaine metabolite, cocaine craving

METHODS:
- Patients responded to newspaper or radio advertisements
- 2 week, non-medication baseline period
- Treatment protocol: 16 weeks
  - Patients assessed by telephone or clinic visit 30 days following their last clinic visit to verify medical safety
- Patient characteristics at baseline assessed using the Addiction Severity Index and the Structured Clinical Interview for DSM-IV (SCID)
- Retention, urine drug testing, cocaine craving, and adverse events measured
  - Urine drug testing collected on Mondays, Wednesdays, and Fridays during baseline and treatment periods
  - Cocaine craving ratings recorded once per week using a visual analogue scale (0= “not at all” to 100= “strongest ever”)
- Compliance with medication monitored using pill counts
- Patients attended clinic thrice weekly to complete measures, provide urine samples, and attend counseling groups
- Blood panels, urinalyses, and ECG conducted at baseline and weeks 4, 8, 12, and 16

STATISTICAL ANALYSES:
- Applied a generalized estimating equation (GEE) model to determine intervention effects
RESULTS:

- 131 volunteers
  - After 2 weeks non-medication screening period, 70 patients randomly assigned to receive baclofen 20 mg TID (n=35) or placebo (n=35)
- No significant demographic differences between groups
- Baclofen patients retained in the protocol a mean (SD) of 56.87(±43.41) days; placebo patients averaged 48.27(±40.57 days); p=0.46
  - Only 9 patients in baclofen group completed 16 week treatment period
  - Only 8 patients in placebo group completed 16 week treatment period
- No statistical significant differences indentified for cocaine use in intent to treat or evaluable groups
  - Post-hoc analysis: Patients on baclofen significantly more likely to provide urine samples that were cocaine metabolite-free between weeks 3 to 8 than patients on placebo (p<0.001)
- GEE solution showed a significant effect of baclofen over placebo in reducing cocaine use as measured using urine drug screening results (p=0.021)
  - Transitional analysis confirmed GEE analysis and identified a strongly significant interaction between baclofen and baseline level of cocaine use (p=0.001)
- No statistically significant difference between patient ratings of cocaine craving for the 24 hours prior to the clinic visit by medication condition as evaluated using GEE
- 3 serious adverse events
  - None judged to be related to study medication
- Patients on baclofen more likely to experience headaches
- Placebo patients took a mean of 69.85%(±22.82%) of their study medication doses
- Baclofen patients took a mean of 72.50%(±22.82%) of their study medication doses
  - Non-significant difference

AUTHOR'S CONCLUSION: “Findings from this study also are limited in that they represent a single efficacy trial of baclofen as a cocaine dependence pharmacotherapy. Results may only generalize to that group of cocaine-dependent individuals who are willing to join an intensive outpatient medication research trial. Yet, the data indicate strongly that a larger trial of baclofen is warranted.”

REVIEWER’S OPINION:

<table>
<thead>
<tr>
<th>STRENGTHS</th>
<th>WEAKNESSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized, placebo-controlled</td>
<td>Preliminary study, small sample size</td>
</tr>
<tr>
<td></td>
<td>Many dropouts</td>
</tr>
<tr>
<td></td>
<td>Not generalizable</td>
</tr>
<tr>
<td></td>
<td>Many post-hoc analyses to find trends</td>
</tr>
</tbody>
</table>
MULTI-CENTER TRIAL OF BACLOFEN FOR ABSTINENCE INITIATION IN SEVERE COCAINE-DEPENDENT INDIVIDUALS

STUDY OBJECTIVE: To test baclofen’s ability to help cocaine patients initiate abstinence

STUDY DESIGN: Multi-site (8 Veterans Affairs sites in United States), double-blind, placebo-controlled

STUDY SUBJECTS:
- **Inclusion Criteria:** Meet DSM-IV criteria for cocaine dependence, at least 18 years of age, and otherwise in good health
- **Exclusion Criteria:** Current dependence on any psychoactive substance other than cocaine, alcohol, nicotine, or marijuana, court ordered treatment for drug dependence, potential for incarceration during the study, psychiatric or neurologic diagnosis, history of electroconvulsive therapy in the prior 3 months, serious medical illness, current medications that could affect or be affected by the action or metabolism of baclofen, pregnancy/lactating

PRIMARY OUTCOME: Weekly mean proportion of days of cocaine non-use as determined by patient self report confirmed with urine assays for cocaine metabolite utilized

SECONDARY OUTCOME(S): Proportion of patients who reduced their days of cocaine use to 75% or less of their frequency use at baseline, or reduced their use to 50% or less of their frequency use at baseline, maximum number of consecutive days of cocaine abstinence

METHODS:
- Study selected patients who were actively using cocaine at the time of study entry and defined as “severely” dependent based on the criterion that they provided 3 or more urine samples positive for cocaine metabolite in the 14 day screening period
- Total of 160 patients enrolled in the study
- Randomized to receive baclofen 20 mg TID or matched placebo for 8 weeks, followed by follow-up assessments for 4 weeks (baclofen n=80, placebo n=80)
- Received weekly psychosocial therapy (1 hour of individual cognitive behavioral therapy (CBT))
- Compliance checked through pill counts
- Each day of study week coded as cocaine “use” or “non-use” based upon self report
  - Confirmed/disproved by urine drug screen results
    - Urine drug screen coded for “new use”
    - Days a subject self-reported using cocaine always scored as use days, regardless of the urine results
- Severity of cocaine dependence assessed by comparing composite scores of the Addiction Severity Index (ASI), Brief Substance Craving Scale (BSCS), Cocaine Selective Severity Assessment (CSSA), and Clinical Global Impression (CGI-S, CGI-I)
  - ASI at screening and weeks 4 and 8
- Occurrences of adverse events collected at each clinic visit

STATISTICAL ANALYSES:
- Generalized Estimation Equations (GEE)
- Intent to treat analysis
RESULTS:
- No demographic differences between groups
  - On average, cohort was 43 years old and 80% male
- Overall retention 67% (no significant difference between rates in the two groups)
- In ITT population, baclofen failed to increase number of cocaine non-use days
  - Same outcome measure also analyzed with additional model terms to control for variations due to site, gender, cocaine use in the 30 days prior to study, and baseline HAM-D score
    - Failed to detect any significant difference (p=0.75)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Baclofen (N=77)</th>
<th>Placebo (N=78)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of patients who reduced cocaine use days to 75% or less of baseline rate</td>
<td>42.9</td>
<td>46.1</td>
<td>0.75</td>
</tr>
<tr>
<td>% of patients who reduced cocaine use days to 50% or less baseline rate</td>
<td>15.6</td>
<td>19.2</td>
<td>0.67</td>
</tr>
<tr>
<td>Longest consecutive period (in days) of cocaine abstinence (SD)</td>
<td>6.1 ± 6.8</td>
<td>7.4 ± 9.7</td>
<td>0.37</td>
</tr>
</tbody>
</table>

- Baclofen did not show any significantly different effect on weekly severity or improvement scores compared to placebo
- Baclofen failed to lessen the severity in cocaine dependence as assessed by CSSA
- Baclofen failed to experience significantly less craving compared to placebo as assessed by BSCS
- No significant differences between the two treatment groups detected when mean change scores in each of the seven components of the ASI were compared
- Baclofen safe and well tolerated
  - 91% of baclofen patients and 90% of placebo patients experienced adverse effects (not significant)

AUTHOR’S CONCLUSION: “This multi-center trial did not succeed in corroborating the findings of previous single-center investigators who identified baclofen as an effective medication for reducing craving for and use of cocaine, particularly those with severe cocaine dependence”

REVIEWER’S OPINION:

<table>
<thead>
<tr>
<th>STRENGTHS</th>
<th>WEAKNESSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized, double-blind, placebo-controlled</td>
<td>Only looked at abstinence initiation, not relapse prevention</td>
</tr>
<tr>
<td>Dose of baclofen</td>
<td>Small sample size</td>
</tr>
<tr>
<td>Greater retention rates than previous RCT</td>
<td>Self-reporting by patients, no family members</td>
</tr>
<tr>
<td>Substance</td>
<td>Study Design</td>
</tr>
<tr>
<td>-----------</td>
<td>--------------</td>
</tr>
<tr>
<td>Alcohol[^12^]</td>
<td>RCT</td>
</tr>
<tr>
<td>Alcohol[^18^]</td>
<td>RCT</td>
</tr>
<tr>
<td>Alcohol[^19^]</td>
<td>RCT</td>
</tr>
<tr>
<td>Alcohol[^20^]</td>
<td>Secondary analysis of RCT</td>
</tr>
<tr>
<td>Alcohol[^21^]</td>
<td>Open label</td>
</tr>
<tr>
<td>Cocaine[^2^]</td>
<td>RCT, Pilot</td>
</tr>
</tbody>
</table>

**REVIEW OF SUBSTANCES STUDIED**
<table>
<thead>
<tr>
<th>Substance</th>
<th>Study Design</th>
<th># of Patients</th>
<th>Study Duration</th>
<th>Baclofen Dose</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine**</td>
<td>RCT</td>
<td>160</td>
<td>8 weeks</td>
<td>20 mg TID</td>
<td>Weekly proportion of days of cocaine non-use, maximum number of consecutive days</td>
<td>% baclofen pts &amp; placebo pts who reduced cocaine use days to 75% or less of baseline: 42.9 &amp; 46.1, respectively (p=0.75); % baclofen pts &amp; placebo pts who reduced cocaine use days to 50% or less of baseline: 15.6 &amp; 19.2, respectively (p=0.67); maximum consecutive days cocaine abstinence baclofen pts &amp; placebo pts: 6.1 ± 6.8 &amp; 7.4 ± 9.7, respectively (p=0.37)</td>
</tr>
<tr>
<td>Methamphetamine**</td>
<td>RCT (2 active arms: baclofen, gabapentin)</td>
<td>88</td>
<td>16 weeks</td>
<td>20 mg TID</td>
<td>Craving, depression symptoms, urine drug screening results</td>
<td>No statistically significant differences in reports of craving between baclofen, gabapentin, or placebo groups (p=0.52); No statistically significant difference among all 3 groups in depression scale scores (p=0.057); no statistically significant difference in urine drug screening results among all 3 groups (p=0.577)</td>
</tr>
<tr>
<td>Nicotine**</td>
<td>RCT</td>
<td>62</td>
<td>9 weeks</td>
<td>20 mg 4 times daily</td>
<td>CPD, Craving</td>
<td>Baclofen &amp; Placebo CPD at baseline: 20.5 ± 2.1 &amp; 20.8 ± 1.4, respectively; Baclofen &amp; Placebo CPD at week 9: 8.1 ± 1.2 &amp; 11.7 ± 2.7, respectively (p&lt;0.05); No significant differences in craving scores between groups at baseline and week 9 (p&lt;0.34 &amp; 0.48, respectively)</td>
</tr>
</tbody>
</table>

OCDS: Obsessive Compulsive Drinking Scale; CAD: Cumulative Abstinent Duration; %HDD: % Heaving Drinking Days; CPD: Cigarettes Per Day

*: Articles discussed during this presentation

**CONCLUSION:**

Baclofen should be considered for substance dependence treatment in doses no more than 20 mg four times daily in patients who have either failed or are not candidates for FDA indicated treatments (i.e. naltrexone, acamprosate, disulfiram).
REFERENCES:

4. Different authors. "Chapter 75. Substance-Related Disorders: Alcohol, Nicotine, and Caffeine" (Chapter).