Varenicline for Alcohol Use Disorder

Learning Objectives:
1. Understand the differences among alcohol abuse, alcohol dependence and alcohol use disorder
2. Analyze current treatment options for alcohol use disorder
3. Understand why varenicline is considered a potential treatment for alcohol use disorder
4. Evaluate the literature regarding varenicline’s role in alcohol use disorder treatment
Epidemiology:

- Alcohol abuse leads to 1.8 million deaths annually worldwide
- Over 700,000 people are in treatment in the United States at any one time
- Direct and indirect costs of alcohol abuse to the United States are estimated at $185 billion annually

Introduction:

- Alcohol is a dose-dependant central nervous system depressant
- Risk factors for alcohol use disorder may include being single, a history of sexual abuse, urban residence or having deceased parents
- Pathogenesis not thoroughly understood, but alcohol may affect NMDA, GABA, glutamine, dopamine and serotonin 1b receptors
  - Possible genetic component involving genes that code for these receptors
- Ninety percent of alcohol is metabolized by the liver and may be excreted by the lungs and in urine or sweat

DSM-IV Criteria for Alcohol Abuse:

- Maladaptive pattern of alcohol abuse leading to clinically significant impairment or distress, as manifested by one or more of the following, occurring within a 12-month period:
  - Recurrent alcohol use resulting in failure to fulfill role obligations at work, school, or home
  - Recurrent alcohol use in situations in which it is physically hazardous
  - Recurrent alcohol-related legal problems
  - Continued alcohol use despite persistent social problems caused by alcohol
  - Symptoms must never have met the criteria for alcohol dependence

DSM-IV Criteria for Alcohol Dependence:

- Maladaptive pattern of alcohol use, leading to clinically significant impairment or distress, as manifested by three or more of the following, occurring in the same 12-month period:
  - Tolerance
  - Withdrawal
  - Alcohol often taken in larger amounts or over a longer period than was intended
  - Persistent desire or unsuccessful efforts to cut down or control alcohol use
  - Much time spent in activities to obtain alcohol, use alcohol or recover from its effects
  - Activities given up or reduced because of alcohol use
  - Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the alcohol

DSM-IV Criteria for Alcohol Dependence:

- Maladaptive pattern of alcohol use, leading to clinically significant impairment or distress, as manifested by three or more of the following, occurring in the same 12-month period:
  - Tolerance
  - Withdrawal
  - Alcohol often taken in larger amounts or over a longer period than was intended
  - Persistent desire or unsuccessful efforts to cut down or control alcohol use
  - Much time spent in activities to obtain alcohol, use alcohol or recover from its effects
  - Activities given up or reduced because of alcohol use
  - Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the alcohol
DSM-V Alcohol Use Disorder (AUD)\textsuperscript{3}

- A problematic pattern of alcohol use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:
  - Alcohol often taken in larger amounts or over a longer period than intended
  - Persistent desire or unsuccessful efforts to cut down or control alcohol use
  - Spending a great deal of time in activities necessary to obtain alcohol, use alcohol or recover from its effects
  - Craving or strong urge to use alcohol
  - Recurrent alcohol use resulting in failure to fulfill major role obligations
  - Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused by the effects of alcohol
  - Recurrent alcohol use in situations in which it is physically hazardous
  - Tolerance
  - Withdrawal
- Early remission: at least 3 but less than 12 months without AUD criteria (except craving)
- Sustained remission: at least 12 months without AUD criteria (except craving)
- Craving indicated as a strong desire to drink that makes it difficult to think about anything else and often results in drinking

\begin{tabular}{|p{\textwidth}|}
\hline
\textbf{Major Changes between DSM-IV and DSM-V:}\textsuperscript{2,3} \\
- DSM-V removes distinction between abuse and dependence \\
  - Same disorder on continuum of abuse \\
  - DSM-IV abuse required one criteria and DSM-IV dependence required three criteria \\
  - DSM-V alcohol use disorder requires two criteria
  - Two – three criteria = mild disorder
  - Four- five criteria = moderate disorder
  - Six or more criteria = severe disorder
- DSM-V removed ‘recurrent legal problems’ from criteria
- DSM-V added ‘craving or strong urge to use alcohol’ to criteria
\hline
\end{tabular}

Repeated high doses of alcohol affect several organ systems and may lead to:\textsuperscript{1}

- Pancreatitis
- Cognitive deficits, memory impairment and degenerative changes in the cerebellum
- Gastritis, stomach ulcers
- Liver cirrhosis
- Cardiomyopathy
- Peripheral neuropathy, anemia, thiamine, folic acid and pyridoxine deficiencies, Wernicke-Korsakoff syndrome and increased rates of esophagus and stomach cancers

\begin{center}
\includegraphics[width=\textwidth]{organ_images}
\end{center}
Management of Alcohol Disorders

- Post-diagnosis, obtain thorough assessments of substance use and prior treatment, medical and psychiatric histories and labs to identify concurrent issues that can be addressed
  - Rule out conditions that are contraindicated with certain AUD medications, such as renal failure or current opioid use
- Assess motivation for change
  - Affects compliance with medications and psychosocial therapy/support
- Role of pharmacologic agents:
  - Potential Benefits:
    - Development of relationship with healthcare provider
    - Enhancement of psychosocial therapy treatment
    - Literature suggests psychosocial intervention increases rates of abstinence and decreases alcohol consumption, but a significant proportion of patients relapse within one year
    - Medication-psychosocial therapy combination is more effective than either alone
  - Controversies:
    - Resistance from third party payers, medications viewed as substitution for self-responsibility, and diagnosis-related stigma

Pharmacologic Agents Used in the Treatment of Alcohol Abuse/Dependence:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Treatment Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acamprosate</td>
<td>666mg by mouth three times daily (lower doses may be effective)</td>
<td>Begin 12 hours to 5 days after abstaining from alcohol and continue indefinitely if needed; fully effective in 5-8 days</td>
</tr>
<tr>
<td>Disulfiram</td>
<td>Initial dose 250mg daily, then 125mg to 500mg daily</td>
<td>Begin following alcohol withdrawal resolution and maintain indefinitely if needed; supervised administration recommended</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>Initial dose 50mg daily, then 50mg to 100mg by mouth daily or 380mg IM every four weeks</td>
<td>If concurrent opioid abuse, begin after patient is opioid-free and maintain indefinitely if needed</td>
</tr>
</tbody>
</table>

- Disulfiram deters a patient from drinking by producing an adverse reaction when alcohol is consumed
  - MOA: inhibits aldehyde dehydrogenase in alcohol metabolism pathway allowing accumulation of acetaldehyde, which causes nausea/vomiting, facial flushing, throbbing headache, chest pain, tachycardia, blurred vision, confusion and hypotension typically lasting thirty to sixty minutes--; may be life-threatening
  - Monitoring: liver function tests
- Naltrexone blocks the effects of exogenous opioids
  - MOA: acts as a competitive antagonist at opioid receptor sites and is thought to attenuate reinforcing effects of alcohol and decrease craving
  - Monitoring: Liver function tests
- Acamprosate reduces alcohol craving
  - MOA: glutamate modulator at the N-methyl-D-aspartate (NMDA) receptor that is thought to reduce alcohol intake
  - Monitoring: suicidal ideation, severe and/or persistent diarrhea
<table>
<thead>
<tr>
<th>Pretreatment Indicators</th>
<th>Medications¹⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acamprosate</td>
</tr>
<tr>
<td></td>
<td>(Campral)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>X</td>
</tr>
<tr>
<td>Significant liver disease</td>
<td>A</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>A</td>
</tr>
<tr>
<td>Current opioid use</td>
<td>A</td>
</tr>
<tr>
<td>Psychosis</td>
<td>A</td>
</tr>
<tr>
<td>Poor medication adherence</td>
<td>C</td>
</tr>
<tr>
<td>High level of craving</td>
<td>A</td>
</tr>
</tbody>
</table>

A = appropriate  C = use with caution  
X = contraindicated  + = particularly appropriate

- Helping patients remain abstinent after alcohol detoxification can be quite challenging and use of these agents remains controversial¹⁴
  - Acamprosate and naltrexone have been shown to be superior to nonpharmacologic therapy alone, but many patients still relapse
  - Disulfiram has not been proven to be as effective and its side effects are poorly tolerated by patients
  - Compliance is generally low and relapse following treatment is common
  - Serotonergic agents such as fluoxetine, citalopram, buspirone and ondansetron, anticonvulsants like topiramate as well as mood stabilizers like lithium have been suggested as possible treatment options for alcohol abuse¹⁴
  - Insufficient efficacy or minimal clinical data have hindered the use of these agents for this indication

**Chantix (varenicline)**

- Background (appendix page 17):
  - FDA-approved in 2006 for smoking cessation and is typically titrated to 1 mg BID for 3-6 months of treatment for this indication¹
  - Partial agonist at neuronal α₄β₂ nicotinic receptors; stimulates dopamine release to a much smaller degree than nicotine resulting in decreased craving and withdrawal
  - Black box warning: serious neuropsychiatric events, depression and suicide
  - Several reports have estimated that 80% of alcohol-dependent people are also smokers⁵
  - Mounting evidence suggests that neuronal nicotinic acetylcholine receptors (nAChRs), which are the targets of nicotine that initiate dependence in smokers, may also play a role in the abusive properties of alcohol⁵
  - Neuronal nAChRs are ligand-gated cation channels that are activated by acetylcholine and nicotine
  - They are expressed in neurons where they presumably directly modulate excitability
  - While ethanol modulates several ligand-gated ion channels including the NMDA, GABA and 5HT3 receptors, it may also modulate nAChRs
  - In vivo studies suggest ethanol modulation of nAChRs may contribute to the mechanism of action of ethanol reward and the common co-abuse of nicotine and alcohol⁵
- Neuronal nAChRs are robustly expressed in the ventral tegmental area of the brain\(^5\)
  - Ethanol and nicotine both increase the firing frequency of ventral tegmental area dopaminergic neurons through nAChRs facilitating dopamine (DA) release
  - Cholinergic signaling through nAChRs also contributes to nucleus accumbens DA release
  - Ethanol and nicotine induced release of DA is critical for the onset and maintenance of alcohol and/or tobacco dependence
  - Identifying the subunit composition of nAChRs involved in alcohol consumption and activation of DA release may highlight new drug targets

<table>
<thead>
<tr>
<th>Varenicline for Alcohol Abuse Trials Overview</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study in Rats</strong></td>
</tr>
<tr>
<td>2007 Steensland(^6)</td>
</tr>
<tr>
<td>Used an operant self-administration model of drinking and reward seeking in rats. Examined the impact of varenicline on ethanol self-administration showing a decrease with acute and chronic administration of varenicline at doses of both 1mg/kg and 2mg/kg. Selectivity for ethanol confirmed with parallel sucrose testing.</td>
</tr>
<tr>
<td><strong>Studies with Heavy Drinking Smokers</strong></td>
</tr>
<tr>
<td>• Conclude varenicline is safe for alcohol users</td>
</tr>
<tr>
<td>2009 McKee(^7,8)</td>
</tr>
<tr>
<td>Double-blind, placebo-controlled trial for effect of varenicline 2mg/day versus placebo on alcohol self-administration in non-alcohol-dependent heavy drinkers who were daily smokers; n=20; varenicline reduced the number of drinks consumed compared to placebo and increased the likelihood of abstaining from drinking.</td>
</tr>
<tr>
<td>2011 Fucito(^9)</td>
</tr>
<tr>
<td>Heavy-drinking smokers were randomly assigned to receive extended four-week pretreatment with varenicline 2mg daily or three weeks placebo plus one-week pretreatment with varenicline 2mg daily for smoking cessation; n=30; participants receiving varenicline all four weeks reported significantly greater reductions in alcohol craving (p=0.03) and fewer heavy drinking days (p=0.06) than placebo group</td>
</tr>
<tr>
<td>2012 Mitchell(^10)</td>
</tr>
<tr>
<td>Discussed Below</td>
</tr>
<tr>
<td><strong>Studies with Non-Smokers</strong></td>
</tr>
<tr>
<td>2013 Plebani(^11)</td>
</tr>
<tr>
<td>Discussed Below</td>
</tr>
<tr>
<td>2013 Litten(^12)</td>
</tr>
<tr>
<td>Discussed Below</td>
</tr>
<tr>
<td>2013 Meszaros(^13)</td>
</tr>
<tr>
<td>Discussed Below</td>
</tr>
</tbody>
</table>
EVALUATION OF LITERATURE

Varenicline Decreases Alcohol Consumption in Heavy-drinking Smokers

Study Objective:
• To determine if varenicline decreases craving and consumption of alcohol in nontreatment-seeking heavy drinkers who were seeking treatment for their smoking

Study Design:
• 12-week, double-blind, placebo-controlled with subjects randomized into one of two treatment groups: varenicline 1mg twice daily (n=33) or placebo twice daily (n=31)
  • Titrated at onset 0.5mg daily for three days, then 0.5mg twice daily for four days
  • Titrated at offset 0.5mg twice daily for two days, then 0.5mg daily for two days
• Subjects invited from Craigslist.org based on cigarette smoking (≥ 10/week) and alcohol consumption (≥ 7 drinks/week for women and ≥ 14 drinks/week for men) to participate in a smoking cessation study
• Initial screening visit included (appendix page 18):
  • Mini-International Neuropsychiatric Interview
  • Alcohol Use Disorders Identification Test (AUDIT)
  • Depression, Anxiety and Stress Scale (DASS)
  • Obsessive Compulsive Drinking Scale (OCDS)
  • Barratt Impulsivity Scale
  • Fagerstrom Test for nicotine dependence
  • Physical exam, ECG, blood draw to determine liver function and pregnancy test for females
• Subjects required to report daily alcohol and cigarette use via online diaries on a secure study server
  • Subjects had until midnight to report substance abuse during previous 24 hours
• Weekly urine samples and ethyl glucuronide (ETG) testing
  • ETG is metabolite formed when ethanol interacts with glucuronic acid and is used to assess alcohol consumption
• Two follow-up visits at weeks 14 and 16
• Subjects paid $20 per visit and $80 for full study completion for $400 maximum payment for the 16-week study

Outcomes:
• Primary Outcomes:
  • Alcoholic drinks per week, cigarettes per week, alcohol craving per week (OCDS)
• Secondary Outcomes:
  • Cumulative cigarettes and alcoholic drinks consumed during treatment period, number of days abstinent and weekly percentage of positive ETG and cotinine screens
    ▪ Cotinine is a metabolite of nicotine and is an indicator of tobacco smoke exposure, detectable up to one week post-exposure

Inclusion Criteria:
• A score of ≥ 8 on the AUDIT, a score of <32 on the DASS, no risk of pregnancy, a BAC < 0.05 to consent and no more than twice weekly use of illicit substances (screened for at each visit)
Exclusion Criteria:
- Physical dependence on alcohol (DSM IV criteria) or previous treatment for alcohol abuse or psychiatric comorbidities (including depression or suicidality)

Statistical Analysis:
- Data from primary outcome measures analyzed using all subjects randomized to treatment and using subjects that completed the 12 weeks of study drug
- Individual change scores (from baseline to week 12) for smoking and drinking were calculated for each subject completing the study and were compared using regression analysis
- Differences were considered significant if p<0.05

Results:
- Sixty-four patients randomized; 35 of 64 completed the 12-week medication cycle and 34 of 64 completed the study through week 16

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Varenicline (n=33)</th>
<th>Placebo (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>29 (range 21-59)</td>
<td>25 (range 21-44)</td>
</tr>
<tr>
<td>Male</td>
<td>18 (55%)</td>
<td>20 (65%)</td>
</tr>
<tr>
<td>Mean baseline drinks per week</td>
<td>35 (range 3-105)</td>
<td>37 (range 5-144)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>24 (73%)</td>
<td>20 (64%)</td>
</tr>
<tr>
<td>Education Level (some college)</td>
<td>12 (36%)</td>
<td>17 (55%)</td>
</tr>
</tbody>
</table>

- No significant difference in rate of retention between both groups (p=0.61)
- Online diary drinking data was positively correlated with AUDIT scores and OCDS scores over the duration of the study drug treatment (p<0.00001)

<table>
<thead>
<tr>
<th>Result</th>
<th>Varenicline</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean cumulative cigarettes smoked</td>
<td>272.97</td>
<td>479.43</td>
<td>0.019</td>
</tr>
<tr>
<td>Mean cumulative drinks</td>
<td>144.60+20.56</td>
<td>224.12+28.9</td>
<td>0.017</td>
</tr>
<tr>
<td>ETG-negative subjects</td>
<td>53.0%</td>
<td>33.3%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Based on n=58 (randomized to treatment), with no distinction given for n in placebo group versus n in varenicline group

- There was no significant difference between groups in all subjects randomized to treatment for the outcome of alcohol craving (p=0.14)
- There was no correlation between average number of drinks consumed per week and average number of cigarettes smoked per week when individual change scores were calculated for each subject
- Five adverse events reported

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Varenicline (number of patients)</th>
<th>Placebo (number of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anger, aggression, nightmares</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Headache and nausea</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Suicidal thinking</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

*all four adverse events in varenicline group occurred while patients were taking concurrent psychostimulants, cocaine or methamphetamine, which might have exacerbated events
Authors’ Conclusions:
• Varenicline reduces reported cumulative consumption of alcohol and ongoing consumption and will have a clinical benefit for heavy drinking smokers
• Varenicline influences both alcohol and cigarette consumption, though these values were not always identically affected by varenicline treatment

Comments:
• Strengths:
  • Riboflavin 25mg added to both drug and placebo capsules to monitor treatment compliance and medication bottles were equipped with Medication Event Monitoring System caps, which recorded the time of each cap removal
• Limitations:
  • Alcohol-dependent subjects and those with comorbid psychiatric conditions were excluded from the trial
  • Potentially inappropriate informed consent because patients had no idea what the study was really looking at
  • Patients’ attempts to quit smoking might have influenced their drinking habits
  • All data presented as cumulative of the group; no individual patient data presented or raw data for primary outcomes
  • Patient dropout rate and inconsistent numbers presented throughout data

Results from a Pilot Clinical Trial of Varenicline for the Treatment of Alcohol Dependence (Plebani, et al. Drug and Alcohol Dependence 2013)11

Study Objective:
• Evaluate efficacy of varenicline treatment for alcohol dependence based on self-reported use gathered using Time-Line Follow Back (TLFB)

Study Design:
• Forty treatment-seeking patients randomized to varenicline 2mg/day (n=19) or matching placebo (n=21) for a 12 week treatment course
  • One research pharmacist assigned group participation and was aware of the medication assignments codes, but all other research personnel were unaware of patient assignments
  • Dose titrated up 0.5mg daily days 1-3, 0.5mg daily days 4-7, then 1mg twice daily
  • Dose titrated down to 1mg/day for the final week of treatment
  • Screening period included physical exam, vital signs and ECG
  • Other psychiatric disorders ruled out with the Mini-International Neuropsychiatric Interview
  • Study medications dispensed in blister packets at weekly clinic visits
  • Subjects were paid $5 for each returned blister pack to facilitate pill counts and earned payments on an escalating scale for attendance and completion of all visit requirements

Outcomes:
• Primary Outcome:
  • Alcohol use based on self-reported alcohol use collected using the TLFB
• Secondary Outcomes
  • Self-reported smoking behavior, mood as measured by the Hamilton Anxiety Scale and Hamilton Depression Scale (HAM-D), global improvement as measured by the nurse-rated Clinical Global Impression-Objective Scale and Clinical Global Impression Scale-Subjective Scale, alcohol craving as measured by the Penn Alcohol Craving Scale (PACS)
Inclusion Criteria:
- Met DSM-IV-TR criteria for alcohol dependence and reported drinking on at least 12 of the past 30 days

Exclusion Criteria:
- Dependence on any other substance (except nicotine) or had active and serious medical or psychiatric illness, were taking psychotropic medications or agents that could interact with varenicline, or had abnormal baseline laboratory findings
- Pregnant or breastfeeding women or women of childbearing age who would not agree to use acceptable birth control methods

Statistical Analysis:
- Baseline measures assessed using t-tests and chi squared tests
- Self-reported drinking results were compared by the generalized estimating equations (GEE) and logistic regression models

Results:
- The two study groups had similar baseline demographics, but there were more African American subjects in the varenicline group as compared to the placebo group (p=0.06)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Varenicline (n=19)</th>
<th>Placebo (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>78.9</td>
<td>90.5</td>
</tr>
<tr>
<td>African American (%)</td>
<td>57.9</td>
<td>28.6</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>44.8</td>
<td>48.1</td>
</tr>
<tr>
<td>Days of alcohol use in past 30 days</td>
<td>18.4</td>
<td>17.6</td>
</tr>
<tr>
<td>Years of alcohol use, lifetime</td>
<td>18.7</td>
<td>21.2</td>
</tr>
<tr>
<td>Baseline smokers</td>
<td>9</td>
<td>8</td>
</tr>
</tbody>
</table>

- There were no significant group effects for weekly days of alcohol use (p=0.67)
- The placebo group had an average of 1.95 times more heavy drinking days per week (p=0.10)
- There was no significant effect for presence/absence of heavy drinking (p=0.16)
- Upon analyzing smokers versus non-smokers, the interactions between smoking group and treatment group were not significant for number of drinking days (p=0.16), number of heavy drinking days (p=0.38) or presence of any drinking (p=0.18)
- Varenicline appears to have been safe and well-tolerated in these patients
  - One “PTSD-like episode” and one report of anxiety were deemed “probably related to the study drug”

Authors’ Conclusions:
- The results of this study suggest varenicline should be investigated in larger trials with more variability in baseline drinking levels
- As smokers have greater reductions in heavy drinking during varenicline treatment, varenicline may be most beneficial for those with both nicotine and alcohol dependence

Comments:
- Strength
  - Blister packs used to facilitate accurate pill counts
  - Analyzed effects of smoking status on drinking
• Limitations
  • “Heavy drinking” was not clearly defined in the study
  • According to the researchers, the subjects for this study were not very heavy drinkers and alcohol use in both groups was low during the trial
  • Dose of varenicline tapered down in last week of treatment
  • Poor presentation of data


**Study Objectives:**
• To determine the efficacy and safety of varenicline in an alcohol-dependent population of smokers and non-smokers

**Study Design:**
• 13-week, multisite, randomized, double-blind, placebo-controlled, parallel-group trial conducted at 5 academic sites in the United States
• Randomly assigned in a 1:1 ratio to receive varenicline or placebo
• Dose titrated: 0.5mg daily days 1 to 3, 0.5mg BID days 4 to 7, then 1mg BID weeks 2 to 13
• Compliance verified by comparing patient self-reporting to pills removed from blister packs and varenicline analyte levels in a subsample of patients
• Baseline visits then five in-clinic visits (weeks 2,4,6,10 and 14) and eight telephone visits (weeks 3, 5, 7, 8, 9, 11, 12 and 13) with a week 16 follow-up telephone interview

**Outcomes:**
• Primary endpoint:
  • Percent heavy drinking days measured weekly during maintenance phase (weeks 2-13)
  • Heavy drinking day defined as four or more drinks per day for women or five or more drinks per day for men
  • One drink defined as 0.5 ounces of absolute alcohol (10 ounces of beer, 4 ounces of wine, 1 ounce of 100-proof liquor)
• Secondary endpoints:
  • Other drinking measures – drinks per day, percent days abstinent, percent very heavy drinking days (eight or more drinks for women, ten or more drinks for men)
  • Alcohol craving (Penn Alcohol Craving Scale)
  • Alcohol-related consequences such as fights, missed work, hangovers and vomiting
  • Cigarettes smoked per day
  • Quality of life (SF-12 Physical and Mental Aggregate Scores)
  • Safety (vital signs, blood chemistries, BAC, adverse events, ECG, neuropsychiatric measures)

**Inclusion Criteria:**
• 18 years of age or older who report drinking at least 28 drinks per week for women or 35 drinks per week for men during 28-day period before consent
• Did not reduce total drinks per week by >50% between 28-day period before consent and 7-day period before randomization
• BAC of 0.000 upon providing consent

**Exclusion Criteria:**
• Past-year DSM-IV dependence on any psychoactive substances other than alcohol/nicotine or history of psychiatric disorders or atherosclerotic cardiovascular disease
• Previous treatment with varenicline
• Previous suicide attempt(s) or past-year suicide risk
Statistical Analysis:
- Intention-to-treat analysis including all patients who took at least one dose
- Continuous outcomes measured at multiple time points analyzed using repeated-measures mixed effects models
- Descriptive statistics – group mean differences for significance by t tests or Wilcoxon rank-sum tests
- Group prevalence rate differences tested via Chi Square test or Fisher exact test
- Least-square means, standard errors and 95% confidence intervals derived from outcomes across the maintenance period
- 170 patients required to complete study to yield 80% power with a 2-tailed t test at a 0.05 significance level

Results:
- 200 patients were randomly assigned; 99 to varenicline and 101 to placebo

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 101)</th>
<th>Varenicline (n = 97*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>69 (68.3%)</td>
<td>71 (73.2%)</td>
</tr>
<tr>
<td>White race</td>
<td>71 (70.3%)</td>
<td>60 (61.9%)</td>
</tr>
<tr>
<td>Mean Age (SD)</td>
<td>45 (12.3)</td>
<td>46 (11)</td>
</tr>
<tr>
<td>Drinks per day (SD)</td>
<td>12.5 (8.9)</td>
<td>14.2 (9.3)</td>
</tr>
<tr>
<td>% Heavy drinking days (SD)</td>
<td>57.8 (35.6)</td>
<td>66.2 (35.0)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>41 (41%)</td>
<td>37 (38.1%)</td>
</tr>
</tbody>
</table>

*Decreased from 99 to 97 because one patient registered at two sites and provided differing data at each site

- 7 varenicline and 12 placebo patients discontinued the study, while 3 varenicline and 6 placebo patients continued the study, but discontinued medication

<table>
<thead>
<tr>
<th>End Points</th>
<th>Placebo (n = 101)</th>
<th>Varenicline (n = 97)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avg percent heavy drinking days</td>
<td>48.4</td>
<td>37.9</td>
<td>0.034</td>
</tr>
<tr>
<td>Avg drinks per day</td>
<td>5.3</td>
<td>4.4</td>
<td>0.031</td>
</tr>
<tr>
<td>Avg percent very heavy drinking days</td>
<td>26.1</td>
<td>17.6</td>
<td>0.047</td>
</tr>
<tr>
<td>Cigarettes per day (weeks 6,10,14)</td>
<td>11.7</td>
<td>7.4</td>
<td>0.002</td>
</tr>
<tr>
<td>PACS score</td>
<td>11.6</td>
<td>9.9</td>
<td>0.011</td>
</tr>
</tbody>
</table>

- Averaged across the maintenance period, the varenicline group experienced significantly lower levels for percent heavy drinking days (primary outcome)
  - Differences were most significant during the last 5 weeks of trial
- No significant difference in percent of subjects who were abstinent, alcohol related consequences or quality of life
- Adverse events:
  - Mild to moderate ADR’s seen in both groups with varenicline having significantly higher rates of nausea, abnormal dreams and constipation
  - Four serious ADR’s – gout and a hernia in the placebo group and back surgery and a shooting death in the varenicline group
Authors’ Conclusions:
• Varenicline significantly reduced the percent of heavy drinking days, craving, drinks per day and drinks per drinking day in both smoking and non-smoking groups
• No significant difference was found between varenicline and placebo in the frequency of abstinent days or in quality of life
• Reductions in drinking warrant further studies to evaluate longer treatment with varenicline and follow-up for sustained effects

Comments:
• Strengths:
  • Overall medication compliance in the study was 95.5% and well assessed
  • Similar outcome measures to those used in trials with disulfiram, naltrexone and acamprosate
  • Appropriate therapeutic doses used
• Limitations:
  • Length of study was too short to determine long-term safety and efficacy
  • Lack of external validity because predominantly male, white, employed, unmarried, middle-aged men and small sample size
  • Patients watched “Take Control” alcohol abuse self-help modules at each clinic visit, which might have influenced their drinking during the week
  • Statistical significance in decrease in drinking may not correlate with clinical significance

Varenicline Treatment of Concurrent Alcohol and Nicotine Dependence in Schizophrenia

Study Objectives:
• To determine the safety and efficacy of varenicline for the treatment of alcohol and nicotine dependence in patients with schizophrenia

Study Design:
• Randomized, double-blind, placebo-controlled trial
• Screening period included physical exam, pregnancy testing, Structured Clinical Interview for DSM-IV disorders, urine drug screen and cotinine and nicotine blood draws
• After screening, participants were seen twice a week the first week of treatment (day 1 and day 4), then weekly over an 8-week treatment period
• Subjects were paid $15/visit
• Varenicline 0.5mg first three days, 0.5mg varenicline twice daily for four days, then 1mg twice daily or matching placebo; subjects were asked to select a smoking quit date within seven days after starting drug
• Motivational interviewing sessions by psychiatrists or psychiatric nurses to assess alcohol use and smoking
• Collateral information obtained from family member or friend weekly by telephone
• Follow-up one month post discontinuation of medication

Outcomes:
• Primary endpoints:
  • Number of standard drinks consumed per week, percent days abstinent from alcohol a month before medication start and during the study and number of cigarettes smoked per week based on Timeline Follow-Back interview
• Secondary endpoints:
  • Fagerstrom Test for Nicotine Dependence, visual analog craving scales for alcohol and nicotine, Clinical Global Impression Scale, Calgary Depression Scale for Schizophrenia, Global Assessment of Functioning, Positive and Negative Symptom Scale, California Verbal Learning Test, Iowa Gambling Test and the Conner’s Continuous Performance Test-Second Addition

Inclusion Criteria:
• Males or females, ages 18 to 69, with a DSM-IV diagnosis of Schizophrenia or Schizoaffective Disorder, receiving outpatient psychiatric treatment
• Currently taking antipsychotic medication for at least 4 weeks
• Current DSM-IV diagnosis of Nicotine Dependence
• Current DSM-IV diagnosis of Alcohol Dependence
• Subject expressed a desire to cut down or quit smoking and drinking
• An average of at least one pack of cigarettes per day (>=20 cigarettes/day) over the 7 days prior to intake
• An average of at least 7 drinks over the 7 days prior to intake

Exclusion Criteria:
• Urine drug test positive for cocaine, opioids or amphetamine at baseline
• Suicide attempt within the last 12 months
• Unstable medical condition or unstable psychiatric illness

Statistical Analysis:
• Endpoints for all patients who received at least one dose of study drug or placebo were compared between groups (placebo versus varenicline)
• Two-sample t tests and Wilcoxon rank sum tests were performed

Results:
• 55 consenting subjects screened; 10 eligible patients underwent randomization (5 to placebo group and 5 to varenicline group); many excluded for positive urine drug screens (n=19), suicide attempts within the last 12 months (n=7) or lack of outpatient psychiatric treatment (n=7)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 5)</th>
<th>Varenicline (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>White/African American</td>
<td>3/2</td>
<td>2/3</td>
</tr>
<tr>
<td>Mean Age (SD)</td>
<td>44 (7)</td>
<td>42 (7)</td>
</tr>
<tr>
<td>Duration of alcohol dependence in years (SD)</td>
<td>25 (7)</td>
<td>25 (11)</td>
</tr>
<tr>
<td>Number of standard drinks per week (SD)</td>
<td>15 (15)</td>
<td>25 (28)</td>
</tr>
<tr>
<td>Number of cigarettes per week (SD)</td>
<td>100 (103)</td>
<td>108 (107)</td>
</tr>
<tr>
<td>% days abstinent from alcohol (SD)</td>
<td>56 (39)</td>
<td>64 (30)</td>
</tr>
</tbody>
</table>

• Dropouts in varenicline group
  • One due to vomiting, irritability and passive suicidal ideation
  • One due to nausea and vomiting
  • One due to incarceration for violating a restraining order
• Dropouts in placebo group
  • One due to headache, irritability, high blood pressure, passive suicidal ideation, anxiety, hallucinations and paranoia in week 3
  • One due to Raynaud’s phenomenon
  • One due to loss of follow-up after visit 6
### End Points (Means at Week Nine)

<table>
<thead>
<tr>
<th>End Points</th>
<th>Placebo (n = 5)</th>
<th>Varenicline (n = 5)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of standard drinks per week (SD)</td>
<td>13 (21)</td>
<td>8 (17)</td>
<td>0.58</td>
</tr>
<tr>
<td>Number of cigarettes per week (SD)</td>
<td>53 (44)</td>
<td>41 (47)</td>
<td>0.46</td>
</tr>
<tr>
<td>% days abstinent from alcohol (SD)</td>
<td>83 (21)</td>
<td>64 (30)</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

- There were no significant changes in positive, negative or general symptoms of schizophrenia during the study.

**Authors’ Conclusion:**

- Varenicline may have poor tolerability when schizophrenia, nicotine dependence and alcohol dependence coexist, largely because of gastrointestinal adverse effects seen in patients.

**Comments:**

- **Strengths:**
  - Attempted implementing study design within a high risk population
- **Limitations:**
  - Small sample size and inadequate statistical power
  - Eight week trial of varenicline is shorter than usual duration of therapy
  - Large difference in drinking habits between two groups
  - “Standard drink” not defined in the study

### Further Studies

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>McKee</td>
<td>Four country survey (n = 4,995) assessing longitudinal associations between smoking cessation medications and alcohol consumption among smokers; varenicline was associated with a reduced likelihood of any drinking compared with nicotine replacement and consuming alcohol once a month or more compared to nicotine replacement or no medication</td>
</tr>
</tbody>
</table>

### SUMMARY

**Clinical Application:**

- Varenicline may benefit smokers with concomitant alcohol use disorder
- Most studies excluded patients with psychiatric disorders and paid patients for participation limiting external validity
- There is insufficient evidence to recommend varenicline in the treatment of alcohol use disorders at this time
- Beneficial future trials may include comparative studies against current FDA approved medications, assessing the efficacy of a varenicline/psychotherapy combination and more long-term follow up

**Pharmacist’s Role in Treatment of Alcohol Use Disorder:**

- Assist in selecting appropriate pharmacologic agents and provide dosing schedules
- Educate patient regarding mechanism of action, dosing and side effects of medication selected
  - Discuss when the medication will become fully effective and how the patient should expect to feel/experience while taking the medication
  - Patient awareness is critical to compliance and successful therapy
- Monitor medication compliance and drug interactions
Literature Cited

Appendix

### Chantix (varenicline) Profile:

**MECHANISM OF ACTION:** partial neuronal α4β2 nicotinic receptor agonist that prevents nicotine stimulation of the dopamine system associated with nicotine addiction

**INITIAL/MAINTENANCE DOSING:**
- Days 1-3: 0.5mg once daily
- Days 4-7: 0.5mg twice daily
- ≥ Day 8: 1mg twice daily for 3-6 months

**RENAL DOSING:**
- CrCl >30 mL/min: no adjustment necessary
- CrCl <30 mL/min: maximum dose 0.5mg twice daily
- ESRD: maximum dose 0.5mg once daily

**BLACK BOX WARNING:** serious neuropsychiatric events (including depression, suicidal thoughts and suicide) have been reported with use

**MONITORING:** behavioral changes and psychiatric symptoms (agitation, depression, suicidal ideation)

**HALF-LIFE:** ~24 hours

**TIME TO PEAK PLASMA CONCENTRATION:** ~3-4 hours

**ADVERSE REACTIONS:** headache, insomnia, abnormal dreams, suicidal ideation, nausea, vomiting

**PREGNANCY CATEGORY:** C

### Abbreviations:

- DSM = Diagnostic and Statistical Manual of Mental Disorders
- AUD = alcohol use disorder
- MOA = mechanism of action
- NMDA = N-methyl-D-aspartate
- FDA = Food and Drug Administration
- nAChRs = nicotinic acetylcholine receptors
- GABA = gamma-aminobutyric acid
- 5HT3 = 5-hydroxytryptamine (serotonin)
- DA = dopamine
- AUDIT = Alcohol Use Disorders Identification Test
- DASS = Depression, Anxiety and Stress Scale
- OCDS = Obsessive Compulsive Drinking Scale
- ETG = ethyl glucuronide
- TLFB = time line follow back
- HAM-D = Hamilton Depression Scale
- PACS = Penn Alcohol Craving Scale
- BID = twice daily
- BAC = blood alcohol content
- ADRs = adverse drug reactions
- ECG = electrocardiogram
**Scales and Tests:**

<table>
<thead>
<tr>
<th>Scale and Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini-International Neuropsychiatric Interview (MINI)</td>
<td>– validated, structured diagnostic psychiatric interview for assessing psychiatric disorders for DSM-IV; takes approximately 15 minutes to administer</td>
</tr>
<tr>
<td>Alcohol Use Disorders Identification Test (AUDIT)</td>
<td>– simple ten question assessment developed by the World Health Organization to determine if a person’s alcohol consumption may be harmful; a score &gt; 8 in men or &gt; 7 in woman indicates a strong likelihood of harmful alcohol consumption</td>
</tr>
<tr>
<td>Depression, Anxiety and Stress Scale (DASS)</td>
<td>– 42 item, 4-point severity, self-report instrument designed to measure the three emotional states of depression, anxiety and stress</td>
</tr>
<tr>
<td>Obsessive Compulsive Drinking Scale (OCDS)</td>
<td>– validated, 14-item instrument that provides two subscale scores that measure cognitive aspects of alcohol craving</td>
</tr>
<tr>
<td>Barratt Impulsivity Scale</td>
<td>– validated, 30-item questionnaire assessing the personality construct of impulsiveness</td>
</tr>
<tr>
<td>Fagerstrom Test for Nicotine Dependence</td>
<td>– standard instrument used to assess intensity of physical addiction to nicotine; the higher the score, the more intense the patient’s physical dependence on nicotine (7-10 points = highly dependent)</td>
</tr>
<tr>
<td>Ethyl glucuronide (ETG) testing</td>
<td>– ethyl glucuronide is a highly sensitive biomarker for alcohol and may be used for alcohol use screening; sensitivity is so strong that even small amounts of alcohol found in some foods and cosmetics can trigger a positive test result</td>
</tr>
<tr>
<td>Cotinine screening</td>
<td>– cotinine is a biomarker for exposure to tobacco</td>
</tr>
<tr>
<td>Time line follow back (TLFB)</td>
<td>– a method used to assess recent substance use and involves asking patients to retrospectively estimate their use within a certain interval of time prior to the interview</td>
</tr>
<tr>
<td>Hamilton Depression Scale</td>
<td>– multiple item questionnaire used to rate the severity of depression in patients already diagnosed as depressed; the higher the score, the more severe the depression</td>
</tr>
<tr>
<td>Clinical Global Impression Scales</td>
<td>– set of 7-point scales commonly used to measure symptom severity, treatment response and efficacy of treatments in patients with mental disorder</td>
</tr>
<tr>
<td>Penn Alcohol Craving Scale</td>
<td>– validated five-item self-administered instrument for assessing alcohol craving; each question scaled from 0-6</td>
</tr>
<tr>
<td>SF-12 Physical and Mental Aggregate Score</td>
<td>– short form, 12-question brief inventory of self-reported mental and physical health</td>
</tr>
<tr>
<td>Calgary Depression Scale for Schizophrenia</td>
<td>– developed to assess the level of depression in schizophrenia</td>
</tr>
<tr>
<td>Global Assessment of Functioning</td>
<td>– scale presented in DSM-IV-TR to rate the social, occupational and psychological functioning of adults</td>
</tr>
<tr>
<td>Positive and Negative Symptom Scale (PANSS)</td>
<td>– relatively brief interview designed to measure symptom severity of patients with schizophrenia</td>
</tr>
<tr>
<td>California Verbal Learning Test (CVLT)</td>
<td>– neuropsychological test of verbal memory that measures various types of recall</td>
</tr>
<tr>
<td>Iowa Gambling Test</td>
<td>– psychological test thought to stimulate real life decision making; used in patients with schizophrenia to determine which brain regions are activated by the task</td>
</tr>
<tr>
<td>Conner’s Continuous Performance Test-Second Addition</td>
<td>– a task-based assessment developed to measure a person’s sustained and selective attention and impulsivity and neurological functioning</td>
</tr>
</tbody>
</table>
