The Smoking Gun: Varenicline for Smoking Cessation in Patients with Mental Health Disorders

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I would feel comfortable dispensing/prescribing varenicline to a patient with a mental health disorder.

- True
- False

Learning Objectives

- Understand the mechanism of action of varenicline
- Understand the reason behind the boxed warning on varenicline
- Evaluate the literature on the use of varenicline in patients with a mental health disorder
- Formulate a recommendation regarding the use of varenicline for smoking cessation in patients with a mental health disorder

Smoking in general population

- Smoking is one of the leading preventable causes of death worldwide
- Suicide rates in smokers is approximately double non-smokers
- Cessation has been associated with increased risk of depression and suicide attempts (SA)
- Nicotine withdrawal is associated with psychiatric disorders independent of smoking cessation treatment

Patients with mental illnesses do not want to quit smoking.

- True
- False
Smoking in mental health population

- In 2010 it was estimated that 53% of adults with serious mental illness (SMI) smoke.
- Individuals with mental health disorders are almost three times as likely to smoke tobacco.
- A common misconception among providers is that patients with mental illnesses do not want to quit.
- Smoking-related mortality attributes to half of all deaths.

Why mental health patients may smoke

- Self-medication hypothesis
- Nicotine may normalize neuronal deficits in schizophrenics
- Dopaminergic effects may ameliorate negative symptoms

Varenicline

- Selective α₄β₂ nicotinic acetylcholine receptor partial agonist and a full agonist of neuronal α₇ nicotinic receptor
- More effective than bupropion and single forms of nicotine replacement therapy (NRT)
- Has been found to increase the odds of long-term abstinence almost 3 times that of placebo
- Adverse events reported in approval trials included nausea, headache, insomnia, and abnormal dreams

Timeline of events

- 2006 – Varenicline (Chantix©) approved by the FDA
- 2007 – Media reports of SI/HI associated with varenicline
- 2008 – Varenicline label revised to carry warning about neuropsychiatric symptoms
- 2009 – FDA requires boxed warning for varenicline
- 2010 – DoD prohibits varenicline use during deployment
- 2014 – FDA panel to reassess boxed warning, votes to keep
- 2016 – European Medicines Agency (EMA) removes warning

Evaluation of the literature

Safety and effectiveness of varenicline in a veteran population with a high prevalence of mental illness

- Purpose:
  - Evaluate the safety profile of varenicline in the veteran population
- Safety assessments:
  - Neuropsychiatric symptoms that led to the FDA warning
- Methods:
  - Retrospective review
  - Telephone clinic contacted Veterans (between 18 and 85 years) who received new varenicline prescriptions
Outcomes:
- Patients were screened for aggression, agitation, extreme drowsiness and suicidal ideation

Results:
- N = 50
- 30% achieved cessation
- 24% discontinued therapy due to an adverse drug event (ADE)
- 20 out of 35 of the failed group had underlying mental illness
- 5 patients reported increase in psychiatric symptoms
- No reports of suicidal ideation (SI)

Discussion:
- Effectiveness trial allowed for a ‘real-world’ evaluation
- Same contact person
- Data was subjective
- Predominantly male population
- Small sample size
- Not generalizable to non-military population

Conclusions:
- Varenicline had low rates of neuropsychiatric ADEs
- Patients should be monitored during cessation

Maintenance treatment with varenicline for smoking cessation in patients with schizophrenia and bipolar disorder

Purpose:
- Evaluate the efficacy of 40 weeks of maintenance varenicline and cognitive behavioral therapy (CBT) in smokers with SMI

Methods:
- 10 community mental health centers
- Inclusion: Outpatients, aged 18-70 w/schizophrenia, schizoaffective disorder, or bipolar disorder, smoking > 10 cigarettes/day, willing to quit, on stable dose of medications for the past 30 days
- Exclusion: Current suicidal/homicidal ideation (SI/HI), active substance abuse, major depressive episode in the prior six months

Study design:
- Patients verified to be abstinent at weeks 11 and 12 of open-label study
- Treatment arms included:
  - Continuation of varenicline 1 mg BID
  - Switch to identical placebo
  - Continued from weeks 12 to 52 and included relapse prevention-focused CBT
- Seven-day point prevalence of abstinence measured at follow-up visits
- Follow-up phase:
  - Treatment discontinued at week 52
  - Biochemically verified abstinence through week 64
  - Telephone follow-up at week 76

Assessments:
- Self-report of smoking behavior, expired carbon monoxide, nicotine withdrawal symptoms, depressive symptoms and manic symptoms
- Adverse Drug Events (ADEs) were reported by general inquiry and targeted questioning for excitement, agitation, anxiety, insomnia, and irritability
- Psychiatric symptoms were evaluated at baseline and study weeks 12, 18, 26, 38, 52, and 64

Outcomes:
- Primary: Smoking abstinence at week 52
- Secondary: Effects on psychiatric symptoms

Results:
- N = 87
- 33 of 40 varenicline and 26 of 47 placebo patients completed study
- Patients in the varenicline group had a longer time to relapse than those in the placebo group
- No effect of treatment assignment on severity of psychiatric symptoms

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (n = 47)</th>
<th>Varenicline (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>12 (26)</td>
<td>11 (28)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>13 (28)</td>
<td>7 (18)</td>
</tr>
<tr>
<td>Agitation</td>
<td>17 (37)</td>
<td>5 (13)</td>
</tr>
<tr>
<td>Euphoria</td>
<td>17 (37)</td>
<td>7 (18)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>11 (24)</td>
<td>11 (28)</td>
</tr>
<tr>
<td>SI</td>
<td>2 (9)</td>
<td>2 (6)</td>
</tr>
</tbody>
</table>
Discussion:
- Point prevalence of abstinence at 1 year was 3 times higher in the varenicline group
- Varenicline was well-tolerated over the 52-week study

Limitations:
- Small sample size
- Loss of 26 patients due to drop out
- Cannot accurately make safety claims due to the small sample size

Conclusion:
- Prolonged abstinence rate among smokers with SMI
- Neuropsychiatric ADEs similar
- Patients should be monitored during cessation

Real-world effectiveness of varenicline versus nicotine replacement therapy in patients with and without psychiatric disorders

Objective:
- Compare the effectiveness and safety of varenicline versus NRT for smoking cessation in patients with and without psychiatric disorders

Methods:
- Retrospective chart review on 194 patients
- Included patients 18 years or older who were prescribed varenicline or NRT
- Excluded patients who had combination therapy (other than NRT), bupropion for treatment other than smoking cessation, pregnant or nursing
- Conducted between July 2007 and December 2010

Results:
- 98 patients treated with varenicline met inclusion criteria
  - Matched to 98 NRT patients
  - Statistically significant differences in baseline characteristics (Table 1)
  - Number of visits and treatment duration did not differ significantly
  - No difference in treatment retention between groups
  - Varenicline showed higher rates of smoking cessation

ADEs:
- Overall reporting of any neuropsychiatric event was higher in the varenicline arm
- Overall reporting of any neuropsychiatric event was higher in those without history of psychiatric disorder

Discussion:
- Varenicline more effective than NRT
- Physicians in the treatment center assessed psychiatric stability prior to prescribing medications for smoking cessation
- Findings may not be generalizable
- ADRs might have been underreported

Conclusions:
- Varenicline was safe and more effective than NRT in patients with and without psychiatric disorders
- Regardless of smoking cessation method chosen and previous psychiatric comorbidities, patients should have close follow-up and be assessed for neuropsychiatric conditions
Varenicline effects on smoking, cognition, and psychiatric symptoms in schizophrenia: A double-blind randomized trial

- **Hypothesis:** Varenicline will improve cognition and reduce smoking in patients with schizophrenia

- **Method:**
  - 8-week double-blind randomized parallel group design study
  - 4 sites: 2 United States, 1 China, and 1 Israel
  - Subjects:
    - DSM-IV diagnosis of schizophrenia or schizoaffective psychosis
    - Treated with antipsychotic therapy
    - February 2009 to January 2013

- **Exclusion criteria:**
  - Currently taking anti-smoking drugs
  - Total PANSS score > 90
  - PANSS depression score > 5
  - Calgary depression scale (CDSS) score > 20
  - Brief (5-10 minutes) counseling about smoking cessation at weekly follow-up sessions
  - Psychiatric medications remained stable during study
  - Weekly medication bottles were used to deliver either placebo or varenicline

- **Evaluations:**
  - Smoking cessation: self-report, breathalyzer CO levels, nicotine and cotinine plasma levels, smoking urges, and cigarette dependence scale
  - Psychopathology: PANSS, SANS, and CDSS
  - Cognition: RBANS and MATRICS Consensus Cognitive Battery
  - Side-effects: side-effect checklist and free form inquiry

- **Results:**
  - N = 87
  - No significant differences between groups
  - Predominantly white and black males with chronic schizophrenia
  - Mean RBANS score was low in both groups
  - Long-term smokers (18-23 years)
  - Baseline low to moderate psychopathology without significant depression

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- **No patient discontinued based on ADEs
- Effects on smoking:**
  - Varenicline significantly reduced smoking and cigarette cravings (Figure 2)
- **Effects on cognition:**
  - Varenicline did not improve cognitive function
- **Effects on psychiatric symptoms:**
  - Varenicline did not show worsening of psychopathology scores
  - Varenicline had a positive effect on the depression component of PANSS, but not on CDSS (Figure 4)
Discussion:
- Varenicline is a safe and effective medication to use in the schizophrenic population for smoking reduction or cessation

Limitations:
- Stable patients
- Not generalizable to female population
- Weekly follow-up and counseling

Conclusions:
- Varenicline appears to be safe in patients with stable SMI
- Close monitoring during cessation indicated

A comparison of neuropsychiatric adverse events during early treatment with varenicline or a nicotine patch

Objective:
- Compare the risk of mental health episodes requiring hospitalization with varenicline versus nicotine patch (NP)

Methods:
- VA patients from May 1st, 2006 through September 30th, 2007 with a prescription for varenicline or NP

Outcomes:
- Primary: Hospital discharge diagnosis of: schizophrenia, bipolar, suicide attempt, PTSD, other psychosis, drug induced mental disorders
- Secondary: New onset mental health disorders/exacerbation in the outpatient setting

Results:
- 11,774 varenicline patients were propensity matched in a 1:2 fashion to NP patients
- The patients were mostly white males, aged 56, with past psychiatric history of PTSD and/or depression
- Hospitalization and overall outpatient visits were not increased in the varenicline cohort
- Subgroup analysis concluded schizophrenic patients on varenicline were seen in outpatient clinic more often (HR=1.27)
- When follow-up was extended to 60 days, more PTSD patients on varenicline were seen in outpatient clinic

Discussion:
- No difference was found in the risks of hospitalization for mental health disorders with varenicline compared to nicotine patch
- Outpatient clinic visits were increased in the varenicline arm for patients with pre-existing schizophrenia and PTSD diagnoses

Limitations:
- SI may have been under reported
- Not generalizable to non-VA population
- No long-term follow-up

Conclusions:
- Varenicline can be prescribed to patients with mental health illnesses
- Special attention should be given to those who are at highest risk for neuropsychiatric events

Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomized, placebo-controlled trial

Objective:
- To compare the relative safety and efficacy of smoking cessation medications in smokers with and without psychiatric disorders

Methods:
- Multinational, multicenter, randomized, double-blind, placebo-controlled and active-controlled trial
- Smokers, aged 18-75, > 10 cigarettes per day, motivated to quit, with or without stable psychiatric disorders
- Excluded: alcohol and other drug use disorders and those at high risk for self-harm or suicidal behavior

8144 patients randomized to receive:
- Varenicline 1 mg BID, bupropion SR 150 mg BID, nicotine patch 21 mg with taper, or placebo

Procedures:
- Smoking cessation counseling of 10 minutes or less was provided at each visit
- Compliance assessed via patch/pill count
- Adverse events:
  - Open-ended questions, observations and Neuropsychiatric Adverse Events Interview (NAEI) performed
  - Psychiatric symptoms were assessed at baseline and throughout study
### Outcomes:

- Adverse events rated by trained investigators (mild/moderate/severe)

### Funding:

- Post-marketing requirement for Pfizer and GlaxoSmithKline
- Designed by sponsor employees (input from authors)
- Lead author had access to all data

### Results:

- Non-psychiatric completers – 3145 (79%)
- Psychiatric completers – 3023 (74%)
- Baseline demographics: 47 year old, white women
  - Mood (71%); anxiety (19%); psychotic (9%); and borderline personality (<1%)
  - 49% taking psychotropic medications at baseline
  - 34% positive for SI and 13% history of suicidal behavior
- Overall neuropsychiatric events in psychiatric group higher versus non-psychiatric group (5.8% versus 2.1% \(p<0.0001\))
- One completed suicide in the placebo group of the non-psychiatric cohort
- Varenicline was superior to nicotine patch, bupropion, and placebo for smoking cessation

### Discussion:

- No significant increase in rates of moderate to severe neuropsychiatric symptoms
- Varenicline showed superior efficacy for smoking cessation
- High generalizability

### Limitations:

- Stable psychiatric patients
- Excluded substance use disorders
- Sample size not large enough to completely rule out rare events (suicide)
- Large drop-out rate

### Conclusions:

- Varenicline does NOT appear to increase the risk for neuropsychiatric events in patients with and without stable psychiatric disorders
- Patients with known psychiatric events should be closely monitored no matter cessation option chosen
- No significant increase in rates of moderate to severe neuropsychiatric symptoms
- Varenicline showed superior efficacy for smoking cessation
- High generalizability
Conclusions

- Varenicline has increased or equal efficacy for smoking cessation in the literature, and the benefits of smoking cessation appear to outweigh the risk of increased neuropsychiatric events in patients utilizing this medication.

- Varenicline should NOT be withheld from appropriate patients with previous psychiatric conditions based on the fear of neuropsychiatric events alone.

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- True
- False