

## Varenicline (CHANTIX) Criteria for Use Updated December 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

*The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.*

*The Product Information should be consulted for detailed prescribing information.*

*See the VA National PBM-MAP-VPE Monograph on this drug at [www.pbm.va.gov](http://www.pbm.va.gov) or <http://vawww.pbm.va.gov> for further information.*

**Exclusion Criteria** *If the answer to ANY item below is met, then the patient should NOT receive varenicline.*

- History of serious hypersensitivity or skin reactions to varenicline
- Suicidal intent, plan or attempt within the past 12 months or current substance use disorder other than nicotine unless varenicline recommended or prescribed by mental health provider (see Issues for Consideration)
- Unstable mental health disorder (e.g. actively experiencing symptoms of psychosis)

**Inclusion Criteria** *The answers to BOTH of the following must be fulfilled in order to meet criteria.*

- Patient desires to quit use of tobacco products and agrees to varenicline after a shared discussion on risks, benefits, and monitoring.
- Patient has one or more of the following:
  - o A previous therapeutic trial of **one** of the following: nicotine replacement therapy, bupropion, or combination therapy (such as nicotine patch plus gum or nicotine patch plus lozenge [Combination Therapy Recommendations](#)).
  - o A previous successful quit attempt using varenicline but has now relapsed.
  - o Difficulty tolerating NRT or bupropion or has a medical contraindication to these medications

### Dosage and Administration

- Begin varenicline 1 week before quit date OR begin varenicline and stop tobacco products between days 8 and 35 of therapy.
- Starting dose: 0.5 mg daily Days 1-3, then 0.5 mg twice a day Days 4-7; then increase to maintenance dose of 1mg twice daily.
- Continue maintenance therapy at 1 mg twice a day for a total of 12 weeks
- An additional 12 weeks of therapy (i.e. a total of 24 weeks) is recommended for successful quitters to increase likelihood of long-term success
- For patients with impaired renal function (estimated creatinine clearance of <30 mL/min) start at 0.5 mg daily for 1 week, then titrate to a maximum of 0.5 mg twice a day.
- For patients with end-stage renal disease on hemodialysis, a maximum dose of 0.5 mg daily if tolerated.
- Consider a temporary or permanent dose reduction in patients who are not tolerating adverse events with full dose.

### Issues for Consideration

- If mental health provider deems treatment with varenicline is appropriate for a patient with suicidal intent, plan, or attempt in the prior 12 months, varenicline may be prescribed.
- The FDA found cases of seizures in people taking varenicline with either no history of seizures or in people with a seizure disorder that was well controlled. The majority of seizures occurred during the first month of therapy.
- Varenicline therapy may lower a patient's tolerance for alcohol, showing signs of increased drunkenness, unusual or aggressive behavior, or memory loss. Patients should be cautioned to decrease the amount of alcohol they drink until they know how they will tolerate the combination of varenicline and alcohol. [FDA Safety Communication 2015](#)
- Tobacco products: Although studied exclusively in patients who smoke tobacco, clinical practice guidelines do not limit use to smoking tobacco; varenicline may be used for other forms of nicotine addiction such as chewing tobacco.
- Cardiovascular risk: Evidence from meta-analyses, real world database studies, and a trial in hospitalized patients with Acute Coronary Syndrome does not show conclusive evidence for or against a cardiovascular safety signal.
- Continued use in patients who are not abstinent from tobacco: Patients who are unable to set a firm quit date may take varenicline and reduce the use of tobacco products. If patient is not abstinent from tobacco product use by week 12 of varenicline therapy, reassess for willingness to quit and devise additional strategies aimed at obtaining and maintaining abstinence. If the veteran is still using tobacco products after 24 weeks of therapy, consider changing to a different therapy (combination NRT or combination bupropion/NRT) and encourage more intensive behavioral treatments (i.e., tobacco cessation groups).

### Renewal/Monitoring Criteria

- Initial prescription limited to 28 day supply. Follow-up via a clinic visit or telephone call within 2-4 weeks of the dispense date of prescription by the provider or a licensed healthcare professional (e.g. clinical pharmacist, registered nurse, social worker, or psychologist) to assess for changes in behavior and abstinence from use of tobacco products (Recommend follow-up in a timely manner to ensure patients receive their next prescription renewal in time).
- Renewals for 28 day supply plus one refill.
- Reinforce instructions to patient and family/friends to immediately report any changes in behavior to the primary care provider or mental health provider. If patient experiences any suicidal or homicidal behavior, instruct to discontinue varenicline and seek immediate medical attention or call the Veteran Crisis Hotline at 1-800-273-8255.
- If therapy continues beyond 12 weeks reassess for abstinence and changes in behavior. Do not treat ~~more~~ for more than 24 weeks.
- If patient or family/friends reports an unexpected change in behavior at any time during therapy, refer to primary care provider or mental health provider.

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## Criteria for Use Update– Varenicline for Smoking Cessation

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### Evidence Summary

**The purpose of this updated review was to address the following questions in order to determine the safe and effective use of varenicline in patients with pre-existing mental health disorders or cardiovascular disease:**

- Is there evidence for suicidal behavior and depression during smoking and/or smoking cessation?
- Is there evidence for an increased incidence of neuropsychiatric events during therapy with varenicline?
- Is there evidence for use of varenicline in patients with a diagnosis of schizophrenia?
- Is there evidence for use of varenicline in patient with a diagnosis of major depression?
- Is there evidence for increased cardiovascular risks from varenicline therapy?

#### **Method:**

- Current VA PBM prescription data for smoking cessation medications was analyzed for duration of therapy and discontinuation rates and reviewed.
- Pub-Med, Cochrane Database of Systematic Reviews, and other OVID Evidence Based Medicine Review databases were searched from 2008 (the last substantive update to the varenicline criteria for use) to July 2015 using various combinations of search terms (e.g. varenicline, mental health, major depression, schizophrenia, suicide, suicidal behavior, smoking cessation, cardiovascular)
- Reference lists from published studies were reviewed for other relevant data.
- References were reviewed and abstracted by members of the Varenicline CFU Working Group (representative members: psychiatrists, psychologists, primary care, smoking cessation pharmacy providers, VA MedSafe, VHA Public Health leadership, National PBM) and discussed with the entire working group in a series of conference calls.
- Individual case reports were not utilized, but case series with analysis were included.
- Following the literature review, the updated varenicline CFU were drafted.

#### **Q1. What is the evidence for suicidal behavior or depression in patients who smoke or during smoking cessation therapy?**

- Do patients who smoke or who are undergoing smoking cessation therapy have an increased risk for suicidal behaviors or depression independent of therapy?
- Data comes primarily from cohort studies, case-control studies, meta-analysis, FDA case reports, population surveys, and national mortality surveys.
- Data from case-control, cohort studies, a meta-analysis of prospective cohort studies, 3 cohorts of American health care workers, national mortality survey data in the U.S., and a population-based prospective cohort study from surveys in southern Germany all find that smoking itself is associated with suicide. Several datasets suggest a dose-response relationship with the number of cigarettes smoked per day and the lifetime duration of smoking associated with increased risk for suicide.

- A biologic explanation for this association may include lower serotonin and monoamine oxidase levels in patients who smoke; nicotine may act like an antidepressant and some evidence suggests antidepressants are associated with an increased risk of suicide.
- The association of smoking cessation with suicide is less clear. Data from a review of case-control and cohort studies assessing a relationship between smoking cessation and suicide was inconclusive.
- Data from a national mortality survey found that quitting smoking was associated with lower odds of suicide.
- Data from the studies specifically evaluating varenicline therapy and risk of suicide found mixed results. The case reports from the FDA Adverse Event Reporting System found a substantial and significant increase in the reported risk of depression and suicidal/self-injurious behavior in patients taking varenicline, but case reports do not prove causation. The large data set from the Clinical Practice Research Link in England found no evidence of increased risk for suicidal behavior in patients prescribed varenicline for smoking cessation compared to nicotine replacement therapy.

Conclusion: Smoking is associated with an increased risk for suicide, likely in a dose-dependent manner. The association of smoking cessation and suicide is inconclusive. Spontaneous adverse event reporting found a significant increase in the reported risk of depression and suicidal/injurious behavior in patients taking varenicline, but data from a large data set of general practice in England found no increased risk for suicidal behavior in patients prescribed varenicline compared to those prescribed nicotine replacement therapy.

**Table 1: Evidence of Suicidal Behavior and/or Depression during Smoking Cessation Therapy**

Reference	Design	# Analyzed	Population	Objective	Results	Study Notes/Limitations
Hughes, et al. 2008 <sup>1</sup>	Review of case-control and cohort studies on association of smoking, smoking cessation, and cessation medications on suicide	N/A	Treatment of smoking cessation and reports of suicide (i.e. thoughts, behaviors, attempts, completed suicides)	Overview of association of smoking, smoking cessation, and cessation medications with suicide	<ul style="list-style-type: none"> <li>• Current smoking is reliably associated with suicide both in case-control and cohort studies</li> <li>• The evidence for the association between smoking cessation, depression, and suicide are characterized as inconclusive</li> <li>• Data used by regulatory agencies to assess the association between bupropion, rimonabant, and varenicline and suicide lack sufficient detail to assess their validity.</li> </ul>	<ul style="list-style-type: none"> <li>• Three explanations are presented for the association: (1) smokers have pre-existing conditions that increase their risk for suicide, (2) smoking causes painful and debilitating conditions that might lead to suicide, and (3) smoking decreases serotonin and monoamine oxidase (MAO) levels.</li> <li>• Current smokers have been found to have lower levels of MAO than never smokers.</li> <li>• Nicotine in smoking may act like an antidepressant, and there is some evidence to suggest that antidepressants increase the risk of suicide.</li> <li>• Most prior data have come from post-hoc analyses.</li> </ul>
Moore, et al. 2011 <sup>2</sup>	Case reports from the FDA's Adverse Event Reporting System 1998-2010	3,249 cases of suicidal/self-injurious behavior or depression.  2,925 for varenicline, 229 for bupropion, 95 for nicotine replacement	Serious case reports for varenicline, bupropion for smoking cessation, and nicotine replacement products	Composite endpoint of suicidal behavior/self-injurious behavior or depression defined.  Ratio of reported suicide/self-injury or depression cases for each drug compared to all other serious events for that drug	<ul style="list-style-type: none"> <li>• Compared to nicotine replacement, the disproportionality results (OR (95% CI)) were varenicline 8.4 (6.8–10.4), and bupropion 2.9 (2.3–3.7).</li> <li>• The disproportionality persisted after excluding reports indicating concomitant therapy with any of 58 drugs with suicidal behavior warnings or precautions in the prescribing information.</li> <li>• An additional antibiotic comparison group showed that adverse event reports of suicidal/self-injurious behavior or depression were otherwise rare in a healthy population receiving short-term drug treatment.</li> </ul>	<ul style="list-style-type: none"> <li>• Case report submissions do not prove causation.</li> <li>• Bupropion cases likely underreported due to lack of specific indication in report</li> <li>• This evidence shows an association, a different type of study design is needed to assess incidence (need appropriate denominator)</li> </ul>

					<ul style="list-style-type: none"> <li>• Varenicline shows a substantial, statistically significant increased risk of reported depression and suicidal/ self-injurious behavior.</li> <li>• Bupropion for smoking cessation had smaller increased risks.</li> </ul> <p>The findings for varenicline, combined with other problems with its safety profile, render it unsuitable for first-line use in smoking cessation.</p>	
Li, et al. 2012 <sup>3</sup>	<p>Meta-analysis of prospective cohort studies</p> <p>Random effects model used to estimate pooled relative risks for complete suicide</p>	2395 cases among 1,369,807 participants between 1966 and 2011.	Never smokers versus current smokers	Evaluate cigarette smoking with suicide risk using random effects model to assess pooled relative risk for completed suicide	<ul style="list-style-type: none"> <li>• Data suggests that cigarettes smoking significantly increased the risk of completed suicide. “Compared with never smokers, the pooled RR was 1.28 (95% CI: 1.001-1.641) for former smokers and 1.81 (95% CI: 1.50-2.19) for current smokers”.</li> <li>• “Significant dose-response relationship was found between smoking and suicide, and the risk of suicide was increased by 24% for each increment of 10 cigarettes smoked per day (RR, 1.24; 95%CI: 1.20-1.28)”</li> <li>• Subgroup analyses showed that the increased suicide risk among current smokers appeared to be consistent, although there was heterogeneity among studies of current smoking (<math>p &lt; 0.001</math>).</li> </ul>	<ul style="list-style-type: none"> <li>• The impact of duration of smoking on risk of suicide could not be determined since most studies did not provide information regarding duration of smoking.</li> <li>• This meta-analysis robustly demonstrated that cigarette smoking is associated with increased risk of completed suicide.</li> </ul>

Thomas et al. 2013 <sup>4</sup>	Prospective cohort study within the Clinical Practice Research Datalink including 349 general practices in England	81,545 users of nicotine replacement, 6,741 bupropion, 31,260 varenicline	Men and women ages 18 and over who used a smoking cessation product between September 2006 and October 2011.	Treated depression  Fatal and non-fatal self-harm within 3 months of the 1 <sup>st</sup> smoking cessation prescription	<ul style="list-style-type: none"> <li>• The authors detected 92 cases of fatal and non-fatal self-harm (326.5 events per 100,000 person years) and 1,094 primary care records of treated depression (6,963.3 per 100,000 person years).</li> <li>• Cox regression analyses showed no evidence that patients prescribed varenicline had higher risks of fatal or non-fatal self-harm (hazard ratio 0.88, 95% confidence interval 0.52 to 1.49) or treated depression (0.75, 0.65 to 0.87) compared with those prescribed nicotine replacement therapy.</li> <li>• There was no evidence that patients prescribed bupropion had a higher risk of fatal or non-fatal self-harm (0.83, 0.30 to 2.31) or of treated depression (0.63, 0.46 to 0.87) compared with patients prescribed nicotine replacement therapy.</li> <li>• Similar findings were obtained using propensity score methods and instrumental variable analyses.</li> </ul>	There is no evidence of an increased risk of suicidal behavior in patients prescribed varenicline or bupropion compared with those prescribed nicotine replacement therapy.
Lucas et al. <sup>5</sup> 2013	Evaluation of 3 large cohort studies	25,033	2 cohorts: female U.S. nurses  1 cohort male U.S. health professionals	Evaluate association between smoking and risk of death from suicide	<ul style="list-style-type: none"> <li>• A total of 457 deaths from suicide were documented.</li> <li>• Death by suicide identified by death certificate</li> <li>• Findings of multivariate analyses- Suicide risk was higher among smokers, in a dose-dependent way with cigarettes smoked per day (CPD)</li> <li>- As compared with never smokers, the pooled multivariate RR of suicide was</li> </ul>	<ul style="list-style-type: none"> <li>• Smoking status was based on self-report and therefore was subject to measurement error.</li> <li>• Participants were not a representative sample of the U.S. population.</li> </ul> <p>Limitations of study- a lack of information about mental illness (such as diagnoses), previous suicide attempts, SUD, etc. Cannot determine causality.</p>

					<p>2.7 times higher among current smokers and was 4 times higher for those who smoked greater than 25 CPD.</p> <ul style="list-style-type: none"> <li>- “The lack of association between duration of smoking or age at start of smoking and suicide suggests that recent smoking behavior, especially the frequency, is associated with suicide risk.”</li> <li>- Findings are consistent with previous cohort study results which reported higher rates of suicide among current smokers.</li> <li>- The results suggested a non-monotonic dose-response association between smoking and suicide risk.</li> <li>- Biological mechanisms such as lower MAO activity and serotonin function in smokers in comparison to non-smokers have been suggested as mechanism for role of smoking in suicide.</li> </ul>	
Balbuena, et al. <sup>6</sup> 2014	Data from the 1993 National Mortality Followback Survey in the United States; case-control design.	989 suicide decedents compared with 3,125 accident and homicide decedents.	White and black patients who every smoked 100 cigarettes in lifetime	To examine if smoking was independently associated with suicide	<ul style="list-style-type: none"> <li>• 3 smoking parameters were compared: lifetime smoking duration, ever quitting, and abstinence duration.</li> <li>• Covariates included depressive symptoms and use of alcohol and drugs.</li> <li>• Data is for males only; no association found with females</li> <li>• In multivariate, fully adjusted analyses, longer lifetime smoking (<math>\geq 41</math> versus <math>\leq 10</math> years) was associated with higher odds of suicide (odds ratio [OR] = 2.26, 95% confidence interval [CI] = 1.30–3.93).</li> <li>• Quitting smoking was</li> </ul>	<ul style="list-style-type: none"> <li>• Bias from next-of-kin reporting</li> <li>• No causal relationship</li> <li>• No clinically validated diagnoses or personality scores</li> <li>• Association between smoking and suicide not found in females</li> <li>• Retrospective analysis of exposures and outcomes of interest</li> </ul>

					<p>associated with lower odds of suicide (OR=.37, CI=.25-.55), as was longer abstinence duration (<math>\geq 11</math> versus <math>\leq 5</math> years) (OR=.33, CI = .21-.52).</p> <ul style="list-style-type: none"> <li>• Longer duration of lifetime smoking was associated with higher odds of suicide, and quitting smoking and longer duration of abstinence were associated with lower odds of suicide.</li> </ul>	
Grucza et al. <sup>7</sup> 2014	<p>Used state-level cigarette excise taxes and smoke-free air policies as antismoking interventions and utilized individual-level data from mortality files and from U.S. population databases to examine suicide risk</p>	N/A	N/A	To investigate the proposition that smoking is a direct risk factor for suicide	<ul style="list-style-type: none"> <li>• In this study, state-level policy interventions involving increases in cigarette excise taxes and the strengthening of smoke-free air laws were found to be associated with a reduction in suicide risk during the 1990s and the early 2000s.</li> <li>• Changes in the relative risk for suicide associated with policy changes were strongest among groups with high smoking prevalence and lowest among groups with low smoking prevalence, suggesting that the effect was a result of policy influence on smoking behavior, rather than confounding with other environmental variables.</li> <li>• Based on these results, it was estimated that a \$1 increase in cigarette excise taxes across the United States could result in a 10.5% relative reduction in risk for suicide.</li> </ul>	Vital statistics data lacked information on smoking
Schneider, et al. <sup>8</sup>	Population-based prospective cohort study	12,888 subjects (6456)	Information was obtained on sociodemographic	To assess the contribution of	<ul style="list-style-type: none"> <li>• Within the follow-up period, a total of 1,449 participants had died, 38 of them by suicide.</li> </ul>	The generalization of these findings to countries with

2014	derived from 3 independent Augsburg surveys in southern Germany	men, 6432 women) were followed up on average for 12.0 years.	characteristics, chronic disease conditions, smoking habits, alcohol consumption, depressive symptoms, personality type, and other psychodiagnostic parameters.	sociodemographic and behavioral factors to the prospective risk of completed suicide in a sample drawn from the general population.	<ul style="list-style-type: none"> <li>● Although several variables were associated with increased risk in the basic analyses, only obesity (HR = 2.73), smoking (HR = 2.23), and living alone (HR = 2.19) remained significantly associated with suicide additionally to male sex (HR = 3.57) and depressed mood (HR = 2.01) in a multivariate analysis.</li> </ul>	different social, economic or cultural conditions may be questioned.
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**Q2. What is the evidence for neuropsychiatric adverse events during smoking cessation with varenicline?**

- Six prospective studies characterized and evaluated neuropsychiatric adverse events during smoking cessation therapy with varenicline.
- One randomized trial found no changes in scores from baseline for depression, anxiety, or nicotine withdrawal in patients treated with varenicline. There was a nonsignificant trend towards higher scores in the varenicline group for aggression and mood states.
- A prospective randomized trial in patients with and without major depression found no difference in neuropsychiatric side effects between varenicline and placebo. Patients with major depression reported more neuropsychiatric adverse events but none were more than moderate.
- A small observational study in patients with stable mental health diagnosis found 1 patient with baseline severe major depression who dropped out from the study. No other serious adverse events were seen.
- A comparative trial of bupropion, varenicline, or placebo found no significant group differences noted for any psychiatric or neurological adverse event.
- A large cohort study in the United Kingdom looking at fatal and non-fatal self-harm also found no increased risk for fatal and non-fatal self-harm or depression between groups when compared to NRT. Based on these results, it is likely that varenicline is safe although there are some issues with the data analysis with regard to propensity matching.
- A pooled study used pooled data from stage II, III, and IV trials (13 trials). Over 3000 varenicline treated patients were included. There were more psychiatric adverse events reported with varenicline but mainly due to sleep disorders.
- A description of 25 case reports of varenicline and neuropsychiatric adverse events found the major reported psychiatric adverse event was mania (40%). 28% reported suicidal ideation.
- A meta-analysis which included over 6000 patients who received varenicline found no difference in the odds ratio for all primary outcomes between varenicline and placebo. Varenicline increased the odds ratio for nightmares, insomnia, and sleep disorders.
- Three retrospective studies in veterans or military personnel are included. There was no difference in the primary outcome of neuropsychiatric adverse events between users of varenicline and nicotine patch in the Military Health System. 2 VA medical centers evaluated neuropsychiatric adverse events with varenicline. One found a 29% increase in mental health encounters only during the varenicline treatment phase. Six patients decompensated with mental health instability including 2 with suicidal ideation. The other VA reported worsening neuropsychiatric adverse events in 4 patients with stable baseline mental health diagnoses.
- A retrospective post marketing evaluation of prescriptions for varenicline in England found an increase in reporting of psychiatric events during treatment period. Depression and anxiety were most common.
- An evaluation of the spontaneous FDA Adverse Event Reporting System for varenicline and other smoking cessation drugs, found an increased overall risk for suicidal/self-injurious behavior and depression with varenicline and to a lesser extent bupropion compared to nicotine replacement therapy.

Conclusion: Prospective studies and a meta-analysis consistently found no difference in neuropsychiatric events with varenicline and its comparators. However, there are limitations to a conclusion due to issues with study designs for all studies. A retrospective study in Military personnel found no difference in the outcome of neuropsychiatric adverse events with varenicline versus nicotine patch, while 2 small studies in veterans noted an increase in reporting of neuropsychiatric adverse events during varenicline therapy. These are not causal but suggest an association. No conclusions can be made from the large post marketing prescription study where there may be an association between varenicline and neuropsychiatric adverse events. The FDA Adverse Event Reporting System

post marketing data, which excluded other drugs known to increase suicidal behavior, also is not causal. The increase in reporting for varenicline may be due to several confounding variables. If evaluating only suicidal/self-injurious behavior, no conclusions can be drawn as these are rare events and no study was powered for rare events.

**Table 2. Evaluation of neuropsychiatric events during varenicline therapy**

Reference	Design	# Analyzed	Population	Objective	Results	Study Notes/Limitations
<b>Prospective Analysis</b>						
Garza, et al. <sup>9</sup> 2011	double-blind randomized placebo-controlled; inpatient design days 14 to 28 with Targeted Quit Date at day 14	857 screened and 110 randomized	Healthy NON CARDIAC AND NON MH patients; Age 33 yo mean	to estimate and characterize NPAEs reported by smokers quitting smoking on either varenicline or placebo.	16 varenicline discontinued therapy vs placebo – mainly due to loss of f/u; were not specific on the details and numbers.  No changes in MADRS/HAM-A/MNWS scores.  OAS-M and POMS for aggression and irritability had trends of higher scores for varenicline vs placebo, but NS.	days 14-28, non smoking inpt facility (although allowed smoking by walking patients outside; this has built barriers to smoking)  -likely not enough power to detect these differences  -Funded by Pfizer
McClure, et al. <sup>10</sup> 2009	prospective randomized trial with phone f/u baseline, 21 post Targeted Quit Date and 4 months comparing “Major Depression (DH+)” vs no “Major Depression (DH-)” on varenicline	DH+=661 DH-=516	Adults Mean age 48	change in stress and depression scores using the Hopkins Symptom Checklist	DH+ - more likely to be female, older, white and unmarried.  No difference in neuropsychiatric side effects.  DH+ did report more neuropsychiatric Sxs: agitation/irritability but none were more than moderate.	Safe in patients without depression.  Likely safe in patients with depression, however given questionable identification of DH+, the data is limiting.
Faessel, et al. <sup>11</sup> 2009	Pharmacokinetics, safety, and tolerability of varenicline in healthy adolescent smokers: multicenter, randomized, double-blind, placebo-controlled, parallel-group study.	N=73	Healthy, adolescent adults	Testing safety and tolerability by having ≥1 dose of Varenicline	Mild agitation in one patient out of 70 individuals.	No conclusion can be drawn from this study.  Pfizer funded

Castle D, et al. <sup>12</sup> 2012	Observational trial	N=14	Stable MH (schizophrenia, schizoaffective D/O, or BD)  Excluded: all unstable psychiatric conditions/medical conditions (uncontrolled DM/cardiac)	varenicline plus participation in the “Healthy Lifestyles” program would be effective and well tolerated as a smoking cessation intervention among persons with psychotic disorders.	1 pt with severe baseline depression dropped due to recurrence, unlikely to be drug related.  No other SAEs.	Not comparative
Cinciripini PM, et al. <sup>13</sup> 2013	Comparative trial comparing Bupropion, varenicline, placebo	N=294	Exclusion: MH/SUD hx	Prolonged abstinence, weekly measures of depression, negative affect and other symptoms of nicotine withdrawal	No significant group differences were noted for any of the psychiatric or neurological adverse events, including anxiety, depression, irritability, disturbances in attention, emotional lability, and sleep disturbances, with the exception of insomnia, which was higher among those receiving bupropion (p=.06).  Higher levels of depression, anxiety and attentional disturbances were observed in the Placebo group, relative to the active drug groups NSS.	Limited due to potential confounding based on exclusion.
Thomas KH, et al. 2013 <sup>14</sup>	Prospective cohort trial in UK  NRT was the main control for Bupropion and varenicline	N=119,546 patient linked to database  N=97,059 patients without linkage to mortality database	Propensity score matching using the following: <ul style="list-style-type: none"><li>• Sex</li><li>• Age</li><li>• Previous psychiatric illness or consultation</li><li>• Previous use of psychotropic drugs</li><li>• Previous self-harm</li><li>• Socioeconomic position</li></ul>	incident episodes of depression  and by fatal and non-fatal self-harm and hospital admission for self-harm	No evidence of increased risk of fatal or non-fatal self-harm or depression between grps when compared to NRT, including propensity score analysis.  Patients prescribed nicotine replacement therapy were more likely than those prescribed the other two drugs to be female and to have a previous history of chronic disease, alcohol misuse,	Likely safe to use but there are limitations in this analysis (7.6% drop in the propensity score analysis with varenicline versus NRT) can be significant. Also if propensity score wasn't matched appropriately, the NRT grp may be a grp with more risk factors for suicidality.

			<ul style="list-style-type: none"> <li>• Drug and alcohol misuse</li> <li>• Major chronic illness using the Charlson index<sup>25</sup></li> <li>• Number of general practice consultations</li> <li>• Whether exposure to the drug occurred before or after 2008, when there was substantial negative media publicity regarding varenicline</li> <li>• Year of first prescription and previous use of a smoking cessation product</li> </ul>		drug misuse, and psychiatric illness including self-harm.	
<b>Pooled studies</b>						
Tonstad S, et al. <sup>15</sup> 2010	Pooled studies from phase II, III and IV trials – 13 studies, 3 excluded: included studies were all randomized and double blinded studies	3091 subjects on varenicline vs 2005 subjects on placebo  Mean age 44 (61% male)	Smokers 18-75 who smoked ≥10 cigarettes day  Exclusion criteria: Any mental health patients were excluded	Incidence and risk of reported psychiatric events from 10 trials  Describe cases of suicidal intention and behavior from 13 trials	More psychiatric adverse events in varenicline but mainly due to sleep disorders and disturbances.  SAEs – one in varenicline due to agitation and hospitalized, complicated by alcohol; Suicide attempt and exacerbation of psychosis in placebo group.  No cases of suicidal behavior or self-injurious behavior in varenicline group.	Not a lot of inclusion/exclusion criteria so potential confounding exists  Pfizer funded for all studies
<b>Review/meta-analyses</b>						
Ahmed, et al. <sup>16</sup> 2013	Descriptive and summary of individual case reports	based on 25 cases reported	N/A	Review and summarize patient case reports of neuropsychiatric events with varenicline and	-severe cases, and hospitalization	Use with caution in MH pts.  -Mania was significant symptom, goes back to more caution in

				determine potential risk factors	-68% were in MH pts  -in 40% of the cases, mania was the major neuropsychiatric symptom; other symptoms were psychosis, 36% (including hallucinations and delirium); suicidal ideation, 28% (including completed suicide); depression, 16%; sleep disturbance/abnormal dreams, 12%; and anxiety, 8%.  Not able to assess risk factors	bipolar pts
Thomas, et al. <sup>17</sup> 2015	Systematic review and meta-analysis	N=11,146 N=6015 varenicline N=5131 placebo	61.3% of participants had no history of psychiatric illness and were from the general population	Primary outcome measures: neuropsychiatric events comprising suicide, attempted suicide, suicidal ideation, and depression  Secondary outcomes: other neuropsychiatric outcomes (abnormal dreams, aggression anxiety, fatigue, insomnia, irritability sleep disorders, somnolence) and death	Odds ratio for all primary outcomes showed no difference between varenicline and placebo.  Varenicline increased the odds for nightmares, insomnia, and sleep disorders.	<ul style="list-style-type: none"> <li>• Study level data so they can't be used as causal as they were unable to determine whether differences in the adverse events were because of greater quit rates in the varenicline group relative to placebo.</li> <li>• -small number of suicides and attempted suicide reported (n=6), we cannot rule out major benefit or adverse effects of varenicline for this outcome</li> <li>• -potential for heterogeneity in the reporting of adverse events discounts previous studies of less sleep disturbances as this analysis had significant power</li> <li>• -likely safe in most patients</li> <li>• -can't rule out whether cessation offsets neuropsych sx's from varenicline</li> </ul>
<b>VA Studies (retrospective)</b>						
Meyer, et al. <sup>18</sup> 2013	Retrospective cohort study using administrative claims database in Military Health System (MHS)		Adults >17 yo  Patients with and without previous neuropsychiatric history using varenicline or	Evaluate the rate of neuropsychiatric events in users of varenicline and nicotine patch in the period prior to first FDA	No difference in primary and secondary outcomes at 30 or 60 days when matched.	<ul style="list-style-type: none"> <li>• Exclusions: a lot of exclusions which include MHS eligibility, stationing overseas; after matching lost about 46% varenicline and 32% NRT</li> <li>• Documentation of ICD9 codes</li> </ul>

			<p>nicotine patch in MHS</p> <p>More females in varenicline group prior to propensity matching</p> <p>Majority had no neuropsychiatric diagnosis in the previous year.</p>	<p>warning based on ICD9 codes</p> <p>Secondary outcome: increase in neuropsychiatric conditions in all settings (including primary care)</p> <p>Propensity score matching</p>	<p>-30 day rate of hospitalization for episodic and mood disorders, as well as personality disorders was greater in varenicline group compared to NRT, not significant.</p>	<p>may not be accurate and would not account for episodic neuropsychiatric episodes</p> <ul style="list-style-type: none"> <li>• Was not able to look at adrs, or discontinuation due to adrs</li> <li>• They calculated 2<sup>nd</sup> fill for refills but didn't include in the analysis</li> </ul> <p>Safe in non MH patients</p>
Campbell, et al. 2010 <sup>19</sup>	Retrospective chart review at Kansas City, Missouri VAMC	PTSD veterans=87 but 9 excluded due to MH instability or MH hospitalization	<p>Age: 54.9</p> <p>Male: 65%</p> <p>42% also had depression, 11% bipolar, 1% schizophrenia</p>	Primary outcome: compare different incidence of mental health encounters	<ul style="list-style-type: none"> <li>• Saw increase in 29% MH encounters during only the varenicline treatment phase (not including varenicline routine f/us).</li> <li>• 6 decompensated with MH instability (2 SI w/in 2 weeks of varenicline) → not documented that varenicline was reason for SI; 2 had worsening depressive episodes after starting medication but resolved.</li> </ul>	<ul style="list-style-type: none"> <li>• Per protocol vs ITT given 9 decompensation not included in analysis</li> <li>• Limitation on causal relationship</li> <li>• Veterans with MH diagnosis receiving varenicline may need more routine monitoring</li> <li>• Potential for increase MH decompensation but not causal</li> </ul>
Cantrell, et al. 2012 <sup>20</sup>	<p>VADERS reports based on the Naranjo ADR Probability Scale</p> <p>Case report series</p>	16 cases but only 4 related to varenicline based on Naranjo ADR Probability Scale	N/A	Identify neuropsychiatric events with varenicline and establish institutional monitoring plan to improve safety and efficacy	<ul style="list-style-type: none"> <li>• Pt 1 PTSD stable → Worsening mood with SI, no intervention needed but MH stable prior to initiation.</li> <li>• Pt 2 PTSD Depression not stable during initiation → Worsening mood with SI, citalopram initiated.</li> <li>• Pt 3 Bipolar stable → Emotional lability, depression, hallucinations, resolved after 20 days.</li> <li>• Pt 4 depressions stable at baseline → Worsening mood and SI.</li> </ul>	<p>Case reports, no causal relationship.</p> <p>Caution for use in bipolar pts, neuropsych can occur in stable pts, but nothing causal.</p>
<b>Retrospective analysis</b>						

Buggy, et al. 2013 <sup>21</sup>	Post-marketing surveillance in England using Modified Prescription Event Monitoring (M-PEM)	questionnaires of 24,508 with 12,159 returned	Male: 43% Psych history: 17%	To examine the pattern of neuropsychiatric events reported in M-PEM	6.2% reported psych events during treatment -913 incidents in 754 pts Depression and anxiety were most common -12 aggression, 8 SI, 1 suicide attempt, 3 overdose other drug, 1 self injury	Observational, survey based, no causal effects can be drawn  Potential for association with varenicline but no conclusions can be drawn.
Moore, et al. 2011 <sup>22</sup>	FDA AERS dataset review 1998-2010  Excluded other concomitant drugs with warnings/precautions for suicidal behavior	N=9575 varenicline N=1751 bupropion N=1917 nicotine N=4047 antibiotics	UK	Primary: suicidal/self-injurious behavior or depression during smoking cessation	Overall risk (compared to nicotine replacement) Varenicline OR 8.4 Bupropion OR 2.9 -Primary end pt (compared to antibiotic group) Varenicline OR 36.6 Bupropion OR 12.5 NRT OR 4.3	Strength was excluding other drugs that have precautions for SI/self-injury.  -the population had higher incidence of primary endpts so could be tobacco users are more likely to have neuropsychiatric effects; with that said, varenicline and bupropion may have higher likelihood of neuropsychiatric disorders and even if not causal, increase reporting can be concerning

NPAE=neuropsychiatric adverse events; MADRS=Montgomery-Asberg Depression Rating Scale; HAM-A=Hamilton Anxiety Scale; MNW=Minnesota Nicotine Withdrawal Scale; OAS-M=modified Overt Aggression Scale; POMS=Profile of Mood States; MH=mental health; SUD=substance use disorder; MH=mental health; VADERS=VA Adverse Drug Event Reporting System; SI=suicidal ideation

**Q3. What is the evidence for use of varenicline in patients with a diagnosis of schizophrenia?**

- In patients with schizophrenia or schizoaffective disorder, varenicline therapy for smoking cessation did not negatively affect positive, negative, or depressive symptoms across 3 prospective randomized trials, 2 observational trials, and 2 meta-analyses.
- In one prospective trial, scores for psychosis and nicotine withdrawal symptoms improved on varenicline therapy.
- Similar results for symptom scores were seen in the observational trials.
- In the meta-analyses, there were no differences in symptom scores between varenicline and placebo. There was inconsistent data on the efficacy of varenicline compared to placebo in terms of smoking cessation: one meta-analysis found no effect of varenicline on quit rates, while the other found inconsistent results.

Conclusion: Varenicline is likely safe to use in patients with stable schizophrenia or schizoaffective disorder.

**Table 3. Varenicline in patients with schizophrenia**

Reference	Design	# Analyzed	Population	Objective	Results	Study Notes/Limitations
Pachas, et al. 2012 <sup>23</sup>	12 week open-label trial of varenicline as part of a 40-week, double-blind, placebo-controlled, relapse-prevention trial in stable outpatient smokers with schizophrenia.	N=112	Age 18-70 Dx of schizophrenia or schizoaffective disorder  Clinically stable on antipsychotic med ≥1 month  ≥10 cigarettes per day	<ul style="list-style-type: none"> <li>• Prospectively assess psychiatric symptoms, adverse events, smoking outcomes</li> </ul>	<p><u>Psych symptoms</u>: no ratings worsened for psychiatric or nicotine withdrawal symptoms from baseline to week 12.</p> <p>Ratings improved for psychosis, nicotine withdrawal.</p> <p>Nausea was the most common adverse event.</p> <p><u>3 serious AEs</u> (voluntary hospitalizations)</p> <p>Pt.1: dysphoric mood assoc. with exacerbation of chronic psychosocial stressors (unrelated to study)</p> <p>Pt. 2: dysphoric mood following 7 weeks abstinence (possible related to study but continued and completed varenicline).</p> <p>Pt 3: paranoia and suicidal ideation (discontinued from study; may have been precipitated by heavy cocaine use)</p> <p><u>Smoking outcomes</u>: 47.3% achieved at least 2 weeks of verified abstinence at week 12; 34% achieved at least 4 weeks of verified abstinence at week 12.</p>	<p>No placebo comparison</p> <p>Limited sample size to detect rare events</p> <p>33% terminated early</p>
Williams, et al. 2012 <sup>24</sup>	Randomized, double-blind, placebo-controlled	N=128 N=85 varenicline N=43 placebo	Age:40.2 Male: 77.4% White: 59.5% Schizophrenia: 70.2% No of yrs smoking: 23.7 Lifetime quit attempts ≥3:	Assess the safety and tolerability of varenicline through measurement of adverse event frequency and changes in psychiatric scales from baseline to week 24 in stable outpatients with schizophrenia or	<p><u>Safety and Tolerability</u></p> <ul style="list-style-type: none"> <li>• Proportion reporting adverse events during treatment and within 30 days of last dose:  86.9 vs 83.7%</li> <li>• Most common AE's: nausea, headache, vomiting</li> </ul>	Unequal randomization of patients reporting higher lifetime incidence of suicidal ideation or behavior at baseline.

			51.2%	schizoaffective disorder who want to stop smoking	<ul style="list-style-type: none"> <li>• Discontinuation due to AE's: no significant difference</li> <li>• Discontinuation due to neuropsychiatric AE's: no significant difference (36.9 vs 32.6%)</li> <li>• 13 serious AE's in varenicline group, ) 0 in placebo; 2 patients had 3 serious AE's (pt1 had depression and suicidal ideation; prior lifetime suicide attempt by overdose. 2<sup>nd</sup> patient overdosed and had a seizure; 4 prior lifetime suicide attempts)</li> <li>• Total, positive, and negative PANSS scores remained stable or slightly decreased from baseline to weeks 12 and 24.</li> <li>• No difference in groups in number who had 10% or greater change in PANSS scores</li> <li>• Both arms, &gt;75% had no change in CGI-I score from baseline.</li> <li>• 1.9% worsened CGI-S scores</li> <li>• Mean Simpson-Angus Rating Scale scores decreased modestly from baseline</li> <li>• Suicidal ideation in 5 varenicline and 3 placebo patients; 1 suicide attempt in varenicline arm.</li> <li>• All patients with suicidal ideation had positive history for suicidal ideation or attempt on C-SSRS.</li> </ul> <p>Smoking cessation</p> <p>7-day point prevalence week 12: 19% vs 4.7% (P=0.046)</p> <p>7-day point prevalence week 24:</p>
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					11.9 vs 2.3% (P=0.09)	
Evins, et al. 2014 <sup>25</sup>	<p>Randomized, double-blind, placebo-controlled, parallel-group</p> <p>Open-label varenicline for 12 weeks; if point prevalence abstinence weeks 11 and 12, randomized to varenicline weeks 12-52 or placebo</p>	<p>N=203 open-label phase</p> <p>N=87 randomized</p> <p>N=40 varenicline</p> <p>N=47 placebo</p>	<p>Outpatients at 10 community mental health centers with schizophrenia, schizoaffective disorder, or bipolar disorder willing to take varenicline and taking a stable dose of antipsychotic or mood stabilizer for 30 days or more</p> <p>Age:18-70</p> <p>Female: 39%</p> <p>White: 74%</p>	<p>7-day point prevalence abstinence rate at week 52.</p>	<p>7-day point prevalence week 52: Odds ratio 6.2; 95%CI 2.2-19.2; P&lt;0.001</p> <p>Weeks 12-52 45% in varenicline group achieved continuous abstinence versus 15% of placebo group</p> <p>Odds ratio 4.6; 95%CI 1.5-15.7: P=0.004.</p> <p>Psychiatric symptoms</p> <p>No effect of assignment on severity of psychiatric symptoms or self-report of health</p> <p>N=11 hospitalized during random phase</p> <p>4 for medical and 7 for psychiatric events</p> <p>2 medical hospitalizations in placebo group</p> <p>5 psychiatric hospitalizations in placebo group and 2 in varenicline group</p>	<p>Small sample size in both open-label and randomized phases.</p> <p>26 randomized patients dropped out before the end of the relapse prevention phase and considered to have relapsed.</p>
Dutra, et al. 2012 <sup>26</sup>	<p>Recruitment from five community mental health centers of subjects with schizophrenia or schizoaffective disorder willing to set a quit date within 2-3 weeks.</p>	<p>N=53</p>	<p>Age 18-70</p> <p>Female: 45.28%</p> <p>Yrs smoking: 26.31</p>	<p>Assess baseline negative symptoms as possible predictors of response to varenicline in a smoking cessation trial of patients with schizophrenia</p>	<p>60.4% met criteria for 14-day point prevalence abstinence at week 12.</p> <p>Negative symptom predictors</p> <p>Patients with lower baseline scores on the affective flattening subscale of SANS (i.e. less severe affective flattening) had larger</p>	

					<p>increases in reward sensitivity. These patients were more likely to attain abstinence with varenicline and cognitive behavioral therapy.</p>	
<p>Liu, et al.<sup>27</sup> 2011</p>	<p>Quasi-experimental in chronic inpatients with schizophrenia</p> <p>Non-randomized control group time series design using an untreated control group and a group choosing to use varenicline</p>	<p>N=30</p> <p>N=15 varenicline</p>	<p>Age: 45</p> <p>Duration of hospitalization (mos): 7.87</p> <p>Stable doses of antipsychotic drugs</p>	<p>Assess if varenicline attenuates abstinence-induced exacerbation of psychopathology and cognitive dysfunction in patients with schizophrenia</p>	<p>Psychiatric outcomes</p> <p>Completers: no difference in baseline HAM-D, HAM-A, PANSS scores between groups</p> <p>Controls: mean HAM-D and HAM-A weeks 2,4,8 significantly higher than at baseline</p> <p>Varenicline: no changes in depression or anxiety before and after abstinence.</p> <p>Degree of exacerbation higher in control group at week 2,4,8 for depression and anxiety.</p> <p>No suicidal ideation or plans in either group.</p> <p>No significant increase or decrease in PANSS subscales scores.</p> <p>Cognitive: No difference between groups at baseline.</p> <p>Performance in control group worsened significantly after abstinence; varenicline had beneficial effect on avoiding</p>	<p>Not randomized</p> <p>Small sample size</p> <p>Chronic male inpatients only</p> <p>Patients grouped themselves which may lead to bias</p>

					deterioration of performance.	
<b>Meta-analysis</b>						
Tsoi, et al. 2013 <sup>28</sup>	Meta-analysis when appropriate.	N=34 trials	Smokers with a diagnosis of schizophrenia. A diagnosis of schizoaffective disorder also allowed.	<ul style="list-style-type: none"> <li>Examine efficacy of different interventions on smoking cessation in patients with schizophrenia</li> <li>Examine efficacy of different interventions on smoking reduction in patients with schizophrenia</li> <li>Assess any harmful effects of different interventions on the mental state of patients with schizophrenia</li> </ul>	<p>Only 2 trials examined the use of varenicline in this population.</p> <p>Some evidence that smokers with schizophrenia were 5 times more likely to abstain from smoking compared to placebo.</p> <p>No evidence that varenicline negatively affected positive, negative or depressive symptoms.</p> <p>However, 2/144 patients reported suicidal ideation or behavior.</p> <p>Did not find consistent evidence that varenicline reduced smoking in people with schizophrenia based on abstinence studies and use for reasons other than smoking cessation in schizophrenia.</p>	<p>One trial only reported preliminary results in a small number of patients.</p> <p>No evidence for sustained abstinence at 6 months.</p> <p>No studies evaluated varenicline primarily for smoking reduction in this population.</p>
Kishi, et al. 2014 <sup>29</sup>	Followed PRISMA guidelines for systematic reviews and meta-analysis	7 studies 6 RCTs with only schizophrenia and 2 RCT with schizophrenia and bipolar disorder	<p>PICO</p> <p>Patients: schizophrenia spectrum</p> <p>Intervention: varenicline adjuvant therapy; Comparator placebo</p> <p>Outcome: efficacy (smoking cessation and psychopathology) and safety (discontinuation rate and side effects)</p>	Effects of varenicline on smoking cessation and psychopathology	<ul style="list-style-type: none"> <li>Varenicline adjuvant therapy not superior to placebo in people with schizophrenia</li> <li>2 individual studies showed varenicline superior to placebo for abstinence</li> <li>Varenicline failed to show superiority over placebo for any symptoms</li> <li>Safety: no difference in discontinuation rates or side effects.</li> <li>Varenicline subjects had less abnormal dreams/nightmares than placebo</li> <li>No difference in side effects</li> </ul>	<p>Included studies differed in inclusion criterion, study duration, primary antipsychotics</p> <p>Sample size of studies was small</p> <p>Most studies were of short duration (8-12 weeks)</p> <p>2 studies did not set cessation dates or include behavioral therapy</p>

					including suicidal ideation, depression.	
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PANSS=Positive and Negative Syndrome Scale; CGI-S=Clinical Global Impressions-Severity of Illness scale; CGI-I=Clinical Global Impression Improvement scale; C-SSRS=Columbia Suicide Severity Rating Scale; SANS=Schedule for the Assessment of Negative Symptoms; HAM-D=Hamilton Scale for Depression; HAM-A=Hamilton Scale for Anxiety; PRISMA=Preferred Reporting Items for Systematic Review and Meta-Analyses

**Q4. Is there evidence for the use varenicline in patients with major depression?**

- In a large, phase IV randomized controlled clinical trial in patients with stably treated or recently remitted major depression, varenicline therapy was superior to placebo in all periods for verified abstinence.
- Both groups had similar changes in depression and anxiety scores on standard scales with a trend toward improved scores.
- Discontinuation rates due to adverse events, incidence of serious psychiatric adverse events, and suicidal ideation or behavior were all similar between the groups.

Conclusion: In stably treated or recently remitted patients with major depression without psychotic features, varenicline treatment for smoking cessation is likely to be effective and safe.

**Table 4. Use of varenicline in major depression**

Reference	Design	# Analyzed	Population	Objective	Results	Study Notes/Limitations
Anthenelli, et al. 2013 <sup>30</sup>	Phase 4, multicenter, parallel, randomized, controlled trial. Participants, investigators, and research personnel blinded to randomization until after final visit.	N=525 N=256 varenicline	Recruited from investigators patients and through media, posters, flyers Age 18-75 At least 10 cigarettes/day DSM-IV for unipolar major depressive disorder without psychotic features. Stable dose of antidepressants for at least 2 months (71% of participants) or had successfully treated major depression in previous 2 years	Primary; carbon-monoxide verified continuous abstinence rate for the last 4 weeks of treatment (weeks 9-12). MADRS and HAM-A at baseline and each visit Suicide risk using SBQ-R and C-SSRS at each visit	Varenicline patients more likely to quit in all periods: Continuous abstinence rates: 9-12 wks 35.9 vs 15.6% 9-24 wks 25 vs 12.3% 9-52 wks 20.3 vs 10.4%  Psych rating scales: Both groups had similar changes in MADRS and HAM-A scores and ratings tended toward slight improvement  Adverse events Discontinuation due to AEs 6.3 vs 7.8%  Psychiatric serious AEs: 2 varenicline patients (psychotic disorder, depression, suicidal ideation) vs 4 placebo patients (intentional self-injury, depression with suicidal ideation, agitation, and depression)  Suicidal ideation or behavior: 6 vs 7.5%	Not powered to detect difference in rare events  Population chosen who were stably treated for or remitted from depression  Excluded patients with psychotic features.  Excluded patients taking medications for mania or psychosis.  Attrition occurred across both arms during 52 week study.

MADRS=Montgomery-Asberg Depression Rating Scale;HAM-A=Hamilton Scale for Anxiety; SBQ-R=Suicidal Behavior Questionnaire Revised; C-SSRS=Columbia Suicide Severity Rating Scale;

### Q5. Is there evidence for increased cardiovascular risks from varenicline therapy?

- The FDA reported that varenicline may be associated with a small increased risk of certain cardiovascular adverse events from the findings of a manufacturer sponsored randomized trial.
- Following that report, a meta-analysis by Singh of 14 RCTs reported that varenicline increased the risk of serious cardiovascular events (i.e. acute myocardial infarction, unstable angina, coronary revascularization, coronary artery disease, arrhythmia, transient ischemic attack, stroke, sudden or cardiac death, and congestive heart failure) with an odds ratio of 1.72 (95%CI 1.09-2.71).
- A second meta-analysis by Prochaska of 22 RCTs, using the same primary outcome as Singh, reported an odds ratio of 1.41 (95%CI 0.82-2.42) for varenicline compared to placebo and concluded varenicline did not increase cardiovascular risk.
- The FDA release the results of a 2<sup>nd</sup> manufacturer sponsored meta-analysis showing a hazard ratio of 1.95 (95%CI 0.79-4.82) for varenicline compared to placebo.
- An retrospective cohort evaluation of claims by Medicare recipients for either varenicline or bupropion found the risk for acute myocardial infarction, stroke, coronary revascularization, or death was not increased for varenicline or bupropion, although the hazard ratio for stroke was a non-significantly increased with wide confidence intervals.
- Kotz used a research database of the National Health Service in England for a retrospective evaluation of cardiovascular or neuropsychiatric events in patients with a prescription for varenicline, bupropion or NRT. Neither drug increase the risk for cardiovascular events compared to NRT. In fact, varenicline decreased the risk for ischemic heart disease, ischemic infarction, heart failure, arrhythmia, depression, and self-harm.
- New data in a group of hospitalized patients immediately following an Acute Coronary Syndrome event who desired to quit smoking and received varenicline or placebo for 12 weeks found varenicline more efficacious than placebo for obtaining point prevalence abstinence at week 24. Although not powered to assess differences in safety, there were no overt cardiovascular safety signals in this high risk population.

Conclusion: The manufacturer of varenicline, at the request of the FDA, produced 2 meta-analyses of their clinical trials and found an increased risk for cardiovascular adverse events during varenicline therapy. 2 independent meta-analyses of similar trials found opposite results: one found an increased risk and one found no increased risk for cardiovascular events. Two real world trials, one from prescription data of Medicare recipients in the USA and one from a research database and prescription data from the National Health Service in England found no increased risk for cardiovascular events with varenicline therapy. Cardiovascular adverse events in these trials would be rare events, and none of the trials was powered to detect such rare events. An efficacy trial in a high risk population of hospitalized patients with Acute Coronary Syndrome found varenicline more effective than placebo with no cardiovascular safety signals identified. While there is a biological plausibility for cardiac adverse events with varenicline, the data from meta-analyses and real world trials is inconclusive as to whether or not a risk exists.

**Table 5. Cardiovascular risks with varenicline therapy**

Study	Design	Patient Population	Results	Limitations	Conclusions																											
Graham, et al 2014 <sup>31</sup>	<p>New user, retrospective cohort using claims comparing patients initiating varenicline or bupropion from Jan 2007-August 2012</p> <p>Age≥65 enrolled in Medicare</p> <p>Excluded:</p> <ol style="list-style-type: none"> <li>&lt;12 mos enrollment</li> <li>Prior tx with either</li> <li>Hosp, SNF, NH or hospice</li> <li>Comorbid psych illness w/wo meds in prev 12 mos</li> <li>Bupropion doses other than 150mg SR BID</li> </ol> <p>Primary Outcome: AMI, stroke, death and composite of the 3</p> <p>Secondary: Coronary revascularization, unstable angina, composite of primary and secondary outcomes</p>	<p>Age 65-74 (82%)</p> <p>Age 75-84 (17.1%)</p> <p>Female: 51%</p> <p>Medical Hx</p> <p>DM 25%</p> <p>HTN 71.5%</p> <p>Microvascular dz 9.1%</p> <p>PV Dz 8.3%</p> <p>AMI 1.2%</p> <p>Cor revascularization 7%</p> <p>HF 5%</p> <p>Other IHD 18%</p> <p>Stroke 4%</p> <p>Concurrent meds:</p> <p>ACEI/ARB 43%</p> <p>B-blocker 32%</p> <p>CCB 26%</p> <p>Statins 52%</p> <p>Nitrates 10%</p> <p>Anticoag 9%</p> <p>Antiplatelet 13%</p>	<p>Median duration of use: 46.5 days V 53.3 days B</p> <p>Continued beyond 1<sup>st</sup> Rx: 30%</p> <p>N=74,824 Varenicline pts N=14,133 Bupropion pts</p> <p>Primary Outcomes:</p> <table border="1"> <thead> <tr> <th></th> <th>V events</th> <th>B events</th> </tr> </thead> <tbody> <tr> <td>Primary</td> <td></td> <td></td> </tr> <tr> <td>AHI</td> <td>133 HR 0.79</td> <td>31</td> </tr> <tr> <td>Stroke</td> <td>83 HR 1.27</td> <td>13</td> </tr> <tr> <td>Death</td> <td>64 HR 0.58</td> <td>23</td> </tr> <tr> <td>Comp</td> <td>256 HR 0.84</td> <td>61</td> </tr> <tr> <td>Secondary</td> <td></td> <td></td> </tr> <tr> <td>Cor Revas</td> <td>463 HR 0.97</td> <td>86</td> </tr> <tr> <td>Comp</td> <td>678 HR 0.92</td> <td>136</td> </tr> </tbody> </table> <p>HR's NSS different</p>		V events	B events	Primary			AHI	133 HR 0.79	31	Stroke	83 HR 1.27	13	Death	64 HR 0.58	23	Comp	256 HR 0.84	61	Secondary			Cor Revas	463 HR 0.97	86	Comp	678 HR 0.92	136	<p>Low use of bupropion in this population.</p> <p>Impossible to exclude patients with depression in bupropion cohort.</p> <p>Low treatment persistence.</p> <p>No data on additional CV risk factors (detailed smoking history, physical activity level, BMI).</p>	<p>In Medicare population risk for AMI, stroke, coronary revascularization, or death not increased in varenicline population versus bupropion</p> <p>HR for stroke with varenicline was NSS increased with wide 95% Confidence intervals.</p>
	V events	B events																														
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Comp	678 HR 0.92	136																														

Singh, et al 2011 <sup>32</sup>	<p>Systematic review and meta-analysis</p> <p>DB RCTs with at least 1 week of follow-up evaluating varenicline as intervention vs placebo that reported on CV events (including no events).</p> <p>Excluded: RCTs with non-tobacco users and observational studies</p> <p>Primary Outcome: Any ischemic or arrhythmic adverse CV events (AMI, unstable angina, coronary revascularization, CAD, arrhythmias, TIAs, stroke, sudden death or CV-related deaths or CHF)</p> <p>Secondary All-cause mortality</p>	<p>14 RCTs identified</p> <p>1 trial smokeless tobacco; the rest were smokers</p> <p>All but 1 excluded pts with a history of CV disease; 1 included pts with stable CV disease</p> <p>13 did not have definition of CV events; evaluated as serious if hospitalized, disabled, or died</p>	<p>Risk of CV events:</p> <p>Meta- analysis showed increased risk for CV events with varenicline</p> <p>Pareto OR 1.72 95%CI 1.09-2.71; <math>I^2=0\%</math></p> <p>Only 5 reported deaths precluding pooling of data (7/4908 in varenicline vs 7/3308 placebo)</p> <p>Sensitivity analysis with (OR 1.67) and without (OR 1.77) a continuity correction found similar results as primary analysis. Sensitivity analysis in trials with active comparators showed similar results (OR 1.67).</p> <p>Excluding 1 trial allowing stable CV disease yielded similar results (OR 2.54 95%CI 1.25-2.94)</p> <p>Excluding trials with doses of varenicline less than 1 mg BID yielded results similar to primary analysis.</p> <p>Only 5 trials reported on specific CV outcomes; analysis of this limited data OR 1.80 (95%CI 0.83-3.91)</p>	<ol style="list-style-type: none"> <li>1. Quality of summary data</li> <li>2. Different populations enrolled in trials</li> <li>3. Low event rates</li> <li>4. No trial powered to detect CV events</li> <li>5. Absence of source data to assess bias</li> <li>6. CV events not pre-specified in trials</li> <li>7. Smokers with unstable CV data excluded from trial-applicability unknown.</li> </ol>	<p>Safety concerns for risk of serious CV events were raised by meta-analysis.</p>
Prochaska, et al 2012 <sup>33</sup>	<p>Systematic review and meta-analysis of treatment emergent CV serious AEs occurring during therapy or within 30 days of discontinuation</p> <p>RCTs study sample of current adult smokers, compared</p>	<p>22 studies identified</p> <p>Majority were male and white patients</p> <p>2 trials studied smokeless tobacco users</p>	<p>Crude rates of CV serious AEs: 0.63% versus 0.47% placebo</p> <p>Risk difference 0.27%</p> <p>95%CI -0.10 -0.63%, P=0.15, <math>I^2=0</math></p>	<p>Peto odds ratio can lead to incorrect conclusions</p>	<p>Found no significant elevation of CV risk with varenicline use</p>

	<p>varenicline and inactive control</p> <p>Exclusion: quasi-experimental or crossover design, laboratory studies without follow-up, studies with adolescents, non-smokers, all received varenicline, comparison with an active control.</p> <p>Summarized increased risk of CV serious AE using risk difference, relative risk, odds ratio, and Peto odds ratio</p>	<p>Smokers averaged 21.5 cigs/day and 25.1 years of smoking</p> <p>13 trials included smokers with current or past CV disease</p> <p>One was among smokers inpatient at a hospital</p> <p>One with smokers with stable CV disease</p> <p>11 had smokers with a history of CV disease</p> <p>Nine excluded patients with a history of CV disease</p>	<p>Relative Risk: 1.40 95%CI 0.82 – 2.39, P=0.22, I<sup>2</sup>=0</p> <p>Odds Ratio: 1.41 95%CI 0.82 – 2.42, P=0.22, I<sup>2</sup>=0</p> <p>Peto odds ratio: 1.58 95%CI 0.90 – 2.76, P=0.11, I<sup>2</sup>=0</p> <p>Sensitivity analyses=4</p> <p>Excluding trials with active CV disease, smokeless tobacco. First exposed to varenicline then randomized to placebo or varenicline maintenance, on unpublished trial. Analysis differed minimally from full analysis.</p> <p>Grouped patients by presence vs absence of events and equal vs unequal number of events to obtain 5 groups: G1 more events in placebo; G2 no events in either; G3 equal events in both; G4 1 or more events in varenicline but none in placebo; G5 events in both but more in varenicline.</p> <p>G3 and 5: evidence for null hypothesis was similar across 4 statistics in G3 but Peto odds ratio underestimated treatment effect in G5.</p> <p>G1 and 4, Peto odds ratio stronger than RR, but OR nearly identical</p>		
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Kotz, et al 2015 <sup>34</sup>	<p>Retrospective cohort study</p> <p>Using QResearch database from National Health Service in England</p> <p>Prescriptions for varenicline, bupropion, or NRT</p> <p>Cardiovascular (ischemic heart disease, cerebral infarction and hemorrhage, heart failure, peripheral vascular disease, and cardiac arrhythmia) and neuropsychiatric events (depression and fatal or non-fatal intentional self-harm) during 6 months of follow-up</p>	<p>Adults 18-100</p> <p>N=106,759 NRT</p> <p>N=6557 bupropion</p> <p>N=51,450 varenicline</p>	<p>Neither bupropion or varenicline increased risk for cardiovascular events compared with NRT (all HR's less than 1.00)</p> <p>Varenicline associated with reduced risk of ischemic heart disease (HR 0.80), cerebral infarction (HR 0.62), heart failure (HR 0.61), arrhythmia (HR 0.73), depression (HR 0.66), and self-harm (HR 0.56).</p> <p>After matching by propensity score, neither bupropion or varenicline showed evidence of increased risk of neuropsychiatric or cardiovascular events compared to NRT.</p>	<p>Observational study design</p> <p>Unmeasured confounders</p> <p>Relied on routinely collected data; some might be incomplete or inaccurate.</p>	<p>In a large observational cohort study, varenicline is unlikely to be associated with increased risk for cardiovascular or neuropsychiatric events compared to NRT.</p>
Eisenberg, et al. 2015 <sup>35</sup>	<p>Randomized, double-blind, placebo-controlled, multicenter</p> <p>Efficacy of varenicline for smoking cessation in patients hospitalized with Acute Coronary Syndrome (myocardial infarction or unstable angina)</p> <p>EVITA=Evaluation of Varenicline In Smoking Cessation for Patients Post-Acute Coronary Syndrome</p>	<p>Adults</p> <p>N=151 varenicline</p> <p>N=151 placebo</p> <p>Treatment for 12 weeks</p>	<p>Primary outcome: point prevalence smoking cessation at 24 weeks- Varenicline 47.3% vs placebo 32.5% ARR=14.8%; NNT=6.8</p> <p>Secondary outcomes</p> <p>Continuous Abstinence weeks 4 and 12 significantly different but not significant at week 24 :35.8% vs 25.8% ≥50% reduction in cigarettes/day at weeks 4, 12, 24 significantly different 67.4% vs 55.6% at week 24</p> <p>Safety</p> <p>Occurrence similar between groups</p> <p>Discontinuation due to AEs similar between groups.</p> <p>Serious Adverse Events</p> <p>A single NP AEs in varenicline patient requiring hospitalization day 25 for depression. No seizures or suicidal ideation</p> <p>19 serious AEs were cardiovascular including 2 deaths, 6 myocardial infarctions, and 5 cases of unstable angina. Composite major</p>	<p>Not powered to examine safety endpoints but enrolled the highest risk population treated with varenicline (90% had myocardial infarction within a few days of beginning treatment). No CV safety signal seen. 2 deaths in varenicline arm within 30 days of stopping therapy require further review.</p> <p>Only enrolled hospitalized patients motivated to quit smoking.</p> <p>Small sample size to adequately address all CV safety.</p>	<p>Varenicline is efficacious for smoking cessation following ACS in hospitalized patients.</p> <p>Less than a third remained abstinent following discharge but patients who received varenicline had higher rates of abstinence versus placebo.</p> <p>Further studies needed for complete safety profile in this population.</p>

			cardiovascular event rates: 4% varenicline and 4.6% placebo. 2 deaths within 30 days of treatment discontinuation and 1 outside of this window in varenicline arm due to CHF(1) 18 days after stopping study medication, sudden death (1)and study medication presumed to have been taken until death, and perforated ulcer (1) 63 days after treatment discontinuation.	Challenging population due to withdrawal from trial or drop-outs.	
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