

Varenicline Criteria for Prescribing

VA Center for Medication Safety, Tobacco Use Cessation Technical Advisory Group, Public Health Strategic Healthcare Group, VA Pharmacy Benefits Management Services, VISN Pharmacist Executives, and Medical Advisory Panel
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The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data 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 individual patient situations.

Introduction:

Varenicline is a second-line medication for smoking cessation in the VA health care system and should be used only for those patients who have failed an appropriate trial of nicotine replacement therapy, bupropion, or combination therapy ([Combination Therapy Recommendations](#)) (or medical contraindication to these medications) within the past year.

In rare instances, varenicline has been associated with violent thoughts, intent or actions toward oneself or others. Prior to starting varenicline, patients should be screened for feelings of hopelessness, which may increase the risk of suicide once the medication is started. Patients should also be screened for current suicidal ideation or intent as well as a history of past suicide attempts. **The recommended screening questions for suicide/violence risk are in Box 1, below:**

Patients who are positive on any of the screening questions require further evaluation by a mental health professional. Patients with active suicidal ideation, plan, or intent should be seen emergently by mental health. In some cases, screening may suggest potential mental illness or suicidality when a subsequent assessment determines otherwise (i.e., a false positive screening test). In those instances, the patient may be eligible for varenicline use per the criteria below.

Patients with suicidal or assaultive thoughts, ideation or behaviors within the past 12 months are not candidates for varenicline until judged to be stable by a mental health professional. A mental health professional should evaluate patients who have made suicide attempts in the distant past to ensure that they are clinically stable prior to starting varenicline and record the evaluation in the patient's chart. **Providers should strongly consider closer monitoring of mental health symptoms for patients with prior suicidality, if they ultimately utilize varenicline.**

Finally, since varenicline use has been associated with severe behavioral changes, **at each renewal** (or at other times, per provider discretion) **patients should be asked the set of questions in Box 2, below.**

Patients who respond in the affirmative to any suicide risk screening questions or who have ideation, plans, or intent to harm others, must not be given a renewal (and/or should be told to stop taking the medication immediately if it is in their possession) and should be provided with urgent mental health assessment. *Possible active suicidal ideation or intent should be evaluated emergently and if the patient is at home he/she may need to be advised to proceed to the nearest source of care (or to call 911) depending on his or her symptoms.*

Box 1: Brief Suicide/Violence Risk Assessment for All Patients Before Initial Prescription

1. Are you feeling hopeless about the present or future?
2. Have you ever had a suicide attempt?
3. Have you had thoughts about taking your life or harming others in the past 12 months? *(if Yes, ask question 4)*
4. Do you have a plan to take your life?

If YES to any question, do not prescribe varenicline. Refer to a mental health professional for a more comprehensive risk assessment. Note that any patient with active suicidality should receive an emergent evaluation.

Box 2: Brief Suicide/Violence Risk Assessment for All Patients Before Prescribing Renewals

Since starting varenicline:

1. Are you feeling hopeless about the present or future?
2. Have you had thoughts about taking your life or harming others *(If yes, ask question 3)*
3. Do you have a plan to take your life or harm others?

If YES to any question, stop and/or do not prescribe varenicline. Refer to a mental health professional for a more comprehensive risk assessment. Note that any patient with active suicidality (or thoughts of harming others) should receive an emergent evaluation.

Exclusions
<ul style="list-style-type: none"> <input type="checkbox"/> Patients who answer in the affirmative to any of the screening questions in Box 1 above (or who do not provide a definitive negative response) and who have not been subsequently evaluated by a mental health expert (and assuming they do not meet other exclusion criteria, below) <input type="checkbox"/> Patients who made a suicide attempt or assaulted others within the past 12 months without a current mental health evaluation judging them to be stable and at low risk for suicidal or assaultive behavior. <input type="checkbox"/> Patients with current and/or persistent suicidal or homicidal ideation or an active plan or intent to harm self or others. <input type="checkbox"/> Patients with a known (diagnosed) but untreated or unstable mental disorder such as, but not limited to, psychotic disorder, bipolar disorder, major depressive disorder, or PTSD. <input type="checkbox"/> Patients without an adequate trial of nicotine replacement therapy, bupropion, or combination therapy (Combination Therapy Recommendations)(or medical contraindication to these medications) within the past year. Varenicline is a second-line treatment option for smoking cessation. (See VA-DoD CPG and USPHS 2008 CPG for adequate trial information) <input type="checkbox"/> Previous successful tobacco cessation following an adequate trial of nicotine replacement therapy, bupropion, or combination therapy (patient should be retried on previously successful treatment) <input type="checkbox"/> Patients whose smoking cessation monitoring is only via non-VA telephone counseling (e.g. a state telephone quit-line) <input type="checkbox"/> Patients who wish to receive varenicline based only on a prescription written by a non-VA prescriber (i.e. not directly monitored for smoking cessation by a VA provider while on varenicline).
Inclusions (Must be determined by the Prescribing Clinician)
<ul style="list-style-type: none"> <input type="checkbox"/> Patients without an active mental health disorder OR <input type="checkbox"/> Patients with a mental health disorder (or prior suicide attempt more than 12 months prior to prescribing) if: <ul style="list-style-type: none"> A) There is an evaluation recorded in the patient chart showing that the mental disorder is clinically stable. AND B) The clinician prescribing varenicline obtains concurrence for varenicline treatment from the patient's mental health provider if the patient is under mental health care; OR, if the patient is not under mental health care, the prescribing clinician should consult with a mental health provider to evaluate the patient for appropriateness to receive varenicline.
Prescription Recommendations and Limits
<ul style="list-style-type: none"> <input type="checkbox"/> Only the Prescribing Clinician may determine eligibility and appropriateness for varenicline after discussing risks and benefits of varenicline with the patient and Mental Health provider, as noted here. <input type="checkbox"/> Prescriptions will have quantity limits of 28 days or less with no refills. Requires monitoring by a Prescribing Clinician at least every 28 days in person or by telephone. As previously noted, Prescribing Clinicians must screen and refer to Mental Health as needed PRIOR to each renewal. <input type="checkbox"/> Initial duration of therapy is 12 weeks with a target quit date within the first 7 days of exposure to varenicline. If the patient stops smoking by week 12, an additional 12 weeks of therapy may increase the likelihood of long term abstinence. A course of therapy with varenicline beyond 24 weeks is unstudied and is not recommended. <p>Re-treatment with varenicline for those who relapse off the agent after initial successful treatment is also unstudied but reasonable (for no more than 24 weeks).</p>
Monitoring
<ul style="list-style-type: none"> <input type="checkbox"/> Prior to starting varenicline, prescribing providers should educate veterans and families/caregivers, if available, about the possibility of changes in behavior or mood and particularly any thoughts of suicide, homicide, assault, self harm, or harm to others. Moreover, the patient should be made aware that these symptoms may occur even when treatment with varenicline has ended. The veteran or family member should immediately report such changes or thoughts to the provider, stop the varenicline if it is still being taken, and/or seek urgent or emergent evaluation and care. In addition, prescribing providers should communicate warnings about driving and operating heavy machinery due to the potential for loss of consciousness, seizures, muscle spasms, visual disturbances or hallucinations (See appendix). The Suicide Prevention Hotline number should be provided to all patients (1-800-273-8255) as a resource if they do experience any thoughts of harming themselves. <input type="checkbox"/> Prescribing provider, or designated licensed individual experienced in behavioral assessment, should monitor each veteran taking varenicline at least monthly with each prescription renewal for changes in behavior and mood (see above) and document the responses (and any actions taken) in the medical record. Monitoring of all patients must include a brief assessment to detect any adverse changes in mood, behavior, and ideation to harm self or others as outlined in Box 2. <input type="checkbox"/> Prescribing provider, or designated licensed individual, should monitor patient for signs of cardiovascular events that may be increased in patients with baseline stable cardiovascular disease: angina pectoris, nonfatal myocardial infarction, new diagnosis of peripheral vascular disease, or need for coronary revascularization and report these as adverse events in CPRS. <input type="checkbox"/> All varenicline prescriptions must be monitored by a VA Provider.

Background Information

Varenicline is a partial agonist at the $\alpha 4\beta 2$ neuronal nicotinic acetylcholine receptor and has an FDA indication as an aid to smoking cessation treatment. The $\alpha 4\beta 2$ neuronal nicotinic acetylcholine receptor releases dopamine in the central nervous system, and activation is thought to mediate dependence, including reinforcement, tolerance, and sensitization of the receptor. As a partial agonist, varenicline binds to the receptor and produces low to moderate levels of dopamine release that reduces craving and withdrawal symptoms. At the same time, varenicline acts as an antagonist, blocking the binding and positive reinforcement effects of smoked nicotine.

Varenicline efficacy and safety were evaluated prior to FDA approval in a drug development program that included 4 trials of 12 weeks duration^{1,2,3,4} and a maintenance trial that allowed for an additional 12 weeks of therapy.⁵ Excluded from these studies were patients with any serious or unstable disease in the past 6 months, patients with a history of depression, psychosis, substance abuse other than nicotine, bipolar disease, panic disorder, or eating disorder. None of these conditions were present in study subjects, yet serious neuropsychiatric adverse events were reported in the 12 week studies including vivid dreaming, nightmares, insomnia, emotional lability (n=1) and acute psychosis (n=1). Atrial fibrillation and other cardiovascular events were also reported as serious adverse events. An additional trial evaluating 52 weeks of therapy with varenicline versus placebo was performed in the United States and Australia. Patients with any clinically significant medical condition or taking antidepressants, antipsychotics, or naltrexone were excluded. The most common serious adverse events were cardiovascular; no neuropsychiatric serious adverse events were reported.⁶ In August of 2007 there were 2 case reports of neuropsychiatric adverse events with varenicline: one case of exacerbation of schizophrenia⁷ and one case of mania in a bipolar patient.⁸

In November of 2007, the FDA released an early communication about an ongoing safety review of varenicline regarding reports of suicidal thoughts and aggressive and erratic behavior in patients who have taken the medication. FDA was reviewing postmarketing cases submitted by Pfizer, Inc, varenicline's manufacturer, describing suicidal ideation and suicidal behavior. FDA's preliminary assessment indicated that many cases presented with new-onset of depressed mood, suicidal ideation, and behavior and emotional changes within days to weeks of starting varenicline. Not all cases had a pre-existing psychiatric illness or had stopped smoking. The role of varenicline is uncertain.

In February of 2008, the FDA issued a Public Health Advisory on varenicline to alert health professionals and patients about new warnings related to changes in behavior, agitation, depressed mood, suicidal ideation, and actual suicidal behavior. Following a review of post-marketing adverse events, FDA requested that Pfizer elevate the prominence of this safety information to the warnings and precautions section of the prescribing information of the labeling. In July 2009, Pfizer revised its patient labeling in the form of an FDA-mandated and approved Medication Guide which by law must be given to patients who are prescribed varenicline.

In the VA, the VA Center for Medication Safety undertook a pharmacovigilance effort with varenicline beginning in September of 2006, collecting and analyzing spontaneous reports of adverse events. Following the first FDA communication in November of 2007, the Center's efforts progressed with an intensive monitoring effort to evaluate events not in the spontaneous reporting system. This included an integrated database monitoring program to pick up events not otherwise captured in the spontaneous reporting database. The initial evaluation of these data was used to formulate the current criteria. These investigations continue.

In June of 2011 the FDA issued a safety communication that varenicline may increase the risk of nonfatal myocardial infarction, angina pectoris, need for coronary revascularization, or new or worsening peripheral vascular disease in patients who have stable, document cardiovascular disease (other than or in addition to hypertension). In a study of 700 patients randomly assigned to varenicline or placebo there was a small numerical increase in the number of cardiovascular events in the varenicline group. The study was not powered to show a statistical difference between the groups based on safety endpoints. The FDA will continue to evaluate the cardiovascular safety of varenicline.

(<http://www.fda.gov/Drugs/DrugSafety/ucm259161.htm>)

Appendix: Patient Information

The following Patient Information should be provided to all patients and family members (if available) when initiating therapy with varenicline:

Please watch for side effects when taking this drug. Contact your health care provider if these occur. It is especially important to seek help if you have a change in your thoughts, behavior or mood. Stop taking the drug and seek help immediately if you have thoughts of harming yourself or others. Be careful driving or using heavy machines if this drug makes you sleepy. If you do experience any thoughts of harming yourself, in addition to stopping the medication and contacting your provider, please also call the VA Suicide Prevention Hotline phone number at 1-800-273-8255 in order to get immediate help. Contact your health care provider if you experience symptoms of cardiovascular (heart) disease, such as shortness of breath or trouble breathing, new or worsening chest pain, or new or worsening pain in legs when walking.

References

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