JAMA Clinical Guidelines Synopsis

Initiating Pharmacologic Treatment in Tobacco-Dependent Adults

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GUIDELINE TITLE Initiating Pharmacologic Treatment in Tobacco-Dependent Adults

DEVELOPER American Thoracic Society

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FUNDING SOURCE American Thoracic Society

TARGET POPULATION Adults with tobacco dependence

MAJOR RECOMMENDATIONS

- For tobacco-dependent adults in whom treatment is being initiated, varenicline is recommended over nicotine patches and bupropion (strong recommendation, moderate certainty in the estimated effects).
- For tobacco-dependent adults in whom treatment is being initiated, varenicline is suggested over e-cigarettes (conditional recommendation, very low certainty).
- In tobacco-dependent adults who are not ready to discontinue tobacco use, clinicians are recommended to begin treatment with varenicline rather than waiting until patients are ready to stop tobacco use (strong recommendation, moderate certainty).
- For tobacco-dependent adults with comorbid psychiatric conditions, varenicline is recommended over a nicotine patch (strong recommendation, moderate certainty).
- For tobacco-dependent adults in whom controller pharmacotherapy (eg, patch or varenicline) is being initiated, extended-duration therapy (>12 weeks) is recommended over standard-duration therapy (6-12 weeks) (strong recommendation, moderate certainty).

Summary of the Clinical Problem

Tobacco use is a chronic relapsing substance use disorder largely sustained by addiction to nicotine.[1] Tobacco use is the leading cause of preventable disease and death in the world, yet it remains prevalent, with 13.7% of US adults reporting current cigarette use in 2018.[2] While 55% of US cigarette smokers have attempted to quit in the previous year, only 7.5% succeed,[2] supporting the need for cessation strategies that provide both behavioral support and an offer of pharmacotherapy during clinical visits.[1] Behavioral support is discussed in detail in the related resources in the Supplement. This guideline[3] was written to provide evidence-based, practical guidance for the component of pharmacotherapy.

Characteristics of the Guideline Source

This statement was commissioned by the American Thoracic Society (ATS) board of directors. Panelists included a patient representative and members from countries outside of North America. Conflicts of interest were disclosed to ATS (**Table**). Important outcomes were determined a priori and systematic reviews were conducted through October 2019 for each key question. Estimated effects for compared outcomes were assessed using the GRADE approach (Grading of Recommendations, Assessment, Development, and Evaluation). The final guidelines were subject to review by ATS editorial staff as well as anonymous peer reviewers, and a patient perspective was included at the end of the document.

Evidence Base

Varenicline is recommended over both the nicotine patch and bupropion. In a systematic review of 11 randomized clinical trials (RCTs), varenicline was associated with increased likelihood of abstinence at 6-month follow-up (relative risk [RR], 1.20 [95% CI, 1.09-1.32]; absolute risk, 40 more/1000 patients) compared with nicotine patch. The use of varenicline plus nicotine patch was associated with increased abstinence compared with varenicline alone (RR, 1.36 [95% CI, 1.07-1.72]; absolute risk, 105 more/1000 patients). In a systematic review of 4 RCTs comparing varenicline with bupropion, varenicline was associated with a greater likelihood of abstinence (RR, 1.30 [95% CI, 1.19-1.42]; absolute risk, 77 more/1000 patients). Compared with 6 to 12 weeks of pharmacotherapy, an extended duration (>12 weeks) was associated with increased abstinence and reduced relapse (hazard ratio, 0.43 [95% CI, 0.29-0.64]).[3]

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Supplemental content

The recommendation for varenicline over e-cigarettes was derived from limited indirect evidence from randomized trials comparing nicotine replacement with either varenicline or e-cigarettes. The panelists considered the removal of the Food and Drug Administration (FDA) black box warning from varenicline in 2016 as well as health risks that have been associated with e-cigarette use.[4] While the evidence for effectiveness is limited, varenicline appears to decrease the risk of severe adverse effects (SAEs) compared with e-cigarettes (RR, 0.32 [95% CI, 0.071-0.82]; absolute risk, 52 fewer/1000 patients).[3]

Among patients not ready to abstain from tobacco, many may be willing to initiate tobacco dependence treatment.[1] To assess the effect of treatment in such smokers, 2 double-blind RCTs with maximum follow-up to 12 months were analyzed. Patients who received varenicline were twice as likely to eventually abstain, com-

Table. Guideline Rating

Standard	Rating
Establishing transparency	Good
Management of conflict of interest in the guideline development group	Good
Guideline development group composition	Good
Clinical practice guideline–systematic review intersection	Good
Establishing evidence foundations and rating strength for each of the guideline recommendations	Good
Articulation of recommendations	Good
External review	Fair
Updating	Fair
Implementation issues	Fair

pared with those receiving placebo (RR, 2.00 [95% CI, 1.70-2.35]; absolute risk, 173 more/1000 patients), although varenicline was associated with a nonsignificant increase in risk for SAEs (RR, 1.75 [95% CI, 0.98-3.13]; absolute risk, 12 more/1000 patients).[3]

Benefits or Harms

Varenicline is an agonist-antagonist, with a mechanism of action theorized to involve a reduction in the rewarding capacity of nicotine. In 2009, based on indirect evidence, the FDA issued a black box warning for varenicline due to potential psychiatric adverse effects. This warning was removed in 2016 based on the EAGLES clinical trial, which did not find an increase in neuropsychiatric adverse events with varenicline compared with placebo or nicotine patch.[5] In a subgroup analysis of adults with comorbid psychiatric conditions, varenicline had a risk of SAEs that was not significantly different than that of the nicotine patch (RR, 0.95 [95% CI, 0.54-1.67]; absolute risk, 1 fewer/1000 patients).[5]

Smoking cessation is associated with myriad health benefits including decreased all-cause mortality and decreased morbidity related to malignancy and cardiopulmonary disease.[1] However, smoking cessation may lead to a nicotine withdrawal syndrome, and the use of pharmacotherapy may increase risk for seizures, depressed mood, and anxiety. In comparisons of varenicline against other modalities, the rates of SAEs were observed to be comparable or lower for varenicline (RR, 0.72 [95% CI, 0.52-1.00]; absolute risk, 3 fewer/1000 patients vs nicotine replacement therapy; RR, 0.81 [95% CI, 0.57-1.16]; absolute risk, 3 fewer/1000 patients for bupropion; and RR, 0.32 [95% CI, 0.071-0.82]; absolute risk, 52 fewer/1000 patients for e-cigarettes).[3] When starting varenicline, patients should be cautioned against potential adverse effects such as nausea, headache, and insomnia, some of which may be dose-dependent.

The panel addressed the common perception that there is limited utility in combining varenicline with nicotine pharmacotherapy, noting that nicotine addiction and smoking behavior are complex and likely involve multiple pathways beyond the mesolimbic reward system. Varenicline plus a nicotine patch was associated with an increase in abstinence compared with varenicline alone, measured as 7-day point-prevalence abstinence at 6 months or later (RR, 1.36 [95% CI, 1.07 to 1.72]; absolute risk, 105 more/1000 patients), with a slight increase in adverse effects.[3] However, the panel made a conditional recommendation for varenicline plus a nicotine patch due to low certainty around estimated SAEs.

Discussion

Despite evidence of health benefits from smoking cessation, clinicians continue to underutilize pharmacologic interventions. Barriers include cost, uneven insurance coverage, and perceived ineffectiveness of pharmacotherapy[6] and lack of tailored guidance for effective implementation. Beyond these factors, certain subgroups may be at greater risk for underutilization of pharmacotherapy, including patients with comorbid psychiatric conditions.[7]

Estimated direct costs for 1 month of therapy are $275 for varenicline, $221 for bupropion, and $139 for nicotine replacement therapy.[8] However, recent data support varenicline as the most cost-effective approach, with a cost-per-quit of $9823 as opposed to a pooled cost-per-quit for all pharmacologic interventions of $19 510.[8]

There is no one-size-fits-all approach to tobacco cessation and, as a limitation, this guideline statement suggests a less nuanced approach. Behavioral therapy is established as an effective treatment and should be part of any treatment plan. In general, smokers benefit from tobacco assessment at each visit, with tailoring of approaches based on the patient's triggers to smoke, level of dependence, readiness to quit, past quit attempts, and personal preferences. Furthermore, because high relapse rates pose an inherent challenge to tobacco cessation, ongoing clinical team engagement and individualized discussion of the benefits of cessation are likely important to success.

Areas in Need of Future Study or Ongoing Research

While this guideline statement[3] recommends varenicline as the most preferred pharmacologic complement to behavioral strategies for smoking cessation, further research is needed to identify strategies to improve prescribing rates, increase adherence, and enhance relapse prevention. Specific patient subgroups, such as highly dependent smokers or those with mood disorders, may potentially benefit from targeted combination therapy (eg, bupropion and varenicline) compared with monotherapy.[9] While the authors consider nicotine patch use in this guideline statement, the guideline meta-analysis did not include generally positive trials studying combined long- and short-acting nicotine replacement.

Finally, identifying novel or alternative therapies to use in patients who have not succeeded with standard pharmacotherapy is needed. An ongoing phase 2 clinical trial is investigating the use of guanfacine, an α_2-adrenergic agonist, to increase rates of abstinence.[10]

ARTICLE INFORMATION

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