Initiating Pharmacologic Treatment in Tobacco-Dependent Adults
An Official American Thoracic Society Clinical Practice Guideline: Executive Summary

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THIS OFFICIAL CLINICAL PRACTICE GUIDELINE WAS APPROVED BY THE AMERICAN THORACIC SOCIETY MAY 2020

Background: Current tobacco treatment guidelines have established the efficacy of available interventions, but they do not provide detailed guidance for common implementation questions frequently faced in the clinic. An evidence-based guideline was created that addresses several pharmacotherapy-initiation questions that routinely confront treatment teams.

Methods: Individuals with diverse expertise related to smoking cessation were empaneled to prioritize questions and outcomes important to clinicians. An evidence-synthesis team conducted systematic reviews, which informed recommendations to answer the questions. The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach was used to rate the certainty in the estimated effects and the strength of recommendations.

Results: The guideline panel formulated five strong recommendations and two conditional recommendations regarding pharmacotherapy choices. Strong recommendations include using varenicline rather than a nicotine patch, using varenicline rather than bupropion, using varenicline rather than a nicotine patch in adults with a comorbid psychiatric condition, initiating varenicline in adults even if they are unready to quit, and using controller therapy for an extended treatment duration greater than 12 weeks. Conditional recommendations include combining a nicotine patch with varenicline rather than using varenicline alone and using varenicline rather than electronic cigarettes.

Conclusions: Seven recommendations are provided, which represent simple practice changes that are likely to increase the effectiveness of tobacco-dependence pharmacotherapy.

Keywords: dependence; pharmacotherapy; smoking; tobacco; treatment

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This Executive Summary is part of the full official ATS clinical practice guideline, which readers may access online at http://www.atsjournals.org/doi/abs/10.1164/rccm.202005-1982ST. Only the Executive Summary is appearing in the print edition of the Journal. The article of record, and the one that should be cited, is: Initiating Pharmacologic Treatment in Tobacco-Dependent Adults: An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med 2020;202:e5–e31.

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This document has an online supplement, which is accessible from this issue’s table of contents at www.atsjournals.org.

Am J Respir Crit Care Med Vol 202, Iss 2, pp 173–183, Jul 15, 2020
Copyright © 2020 by the American Thoracic Society
DOI: 10.1164/rccm.202005-1982ST
Internet address: www.atsjournals.org

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Summary of Recommendations

1. For tobacco-dependent adults in whom treatment is being initiated, we recommend varenicline over a nicotine patch (strong recommendation, moderate certainty in the estimated effects). Remarks: To promote adherence to pharmacologic therapy, providers should be prepared to counsel patients about the relative safety and efficacy of varenicline treatment compared with a nicotine patch.

2. For tobacco-dependent adults in whom treatment is being initiated, we recommend varenicline over bupropion (strong recommendation, moderate certainty in the estimated effects).

3. For tobacco-dependent adults in whom treatment is being initiated, we suggest varenicline plus a nicotine patch over varenicline alone (conditional recommendation, low certainty in the estimated effects).

4. For tobacco-dependent adults in whom treatment is being initiated, we suggest varenicline over electronic cigarettes (conditional recommendation, very low certainty in the estimated effects). Remarks: The recommendation’s strength reflects very low certainty in the effects used to derive the recommendation. After our evidence synthesis, new evidence emerged regarding serious adverse effects of electronic cigarettes. If these serious adverse effects continue to be reported, the strength of the recommendation should be reevaluated. Note that this recommendation is intended for treatment of tobacco dependence under the supervision of a clinician; it should not be extrapolated to unsupervised treatment or recreational use.

5. In tobacco-dependent adults who are not ready to discontinue tobacco use, we recommend that clinicians begin treatment with varenicline rather than waiting until patients are ready to stop tobacco use (strong recommendation, moderate certainty in the estimated effects).

6. For tobacco-dependent adults with comorbid psychiatric conditions, including substance-use disorder, depression, anxiety, schizophrenia, and/or bipolar disorder, for whom treatment is being initiated, we recommend varenicline over a nicotine patch (strong recommendation, moderate certainty in the estimated effects).

7. For tobacco-dependent adults for whom treatment is being initiated with a controller, we recommend using extended-duration (>12 wk) over standard-duration (6–12 wk) (strong recommendation, moderate certainty in the estimated effects).

Introduction

In 1988, the U.S. Surgeon General described tobacco use as the cardinal sign of addiction to nicotine (1). Eight years later, the USPHS published the first comprehensive tobacco-dependence treatment guideline, establishing a new paradigm for clinical care (2, 3). As a result, a first principle of clinical practice was established: all patients who use tobacco should receive treatment for their dependence, rather than simply being encouraged to stop.

This guideline expands on the USPHS foundation. It answers pressing clinical questions regarding the initiation of tobacco-dependence pharmacotherapy. The goal is to improve patient-centered care for tobacco dependence by identifying a single evidence-based pathway that balances important outcomes, including short- and long-term tobacco abstinence and serious adverse events (SAEs), while accounting for important clinical variability. (Figure 1) It was not possible to include all possible pharmacotherapy combination choices nor was it feasible to account for all possible variations encountered in practice. This guideline was created with the assumption that accepted foundations of tobacco-dependence treatment are already in practice (Box 1). The target audience for the recommendations in our guideline includes patients, physicians, other clinicians, nurses, and policy makers.

Disclaimer

It is important to realize that guidelines cannot account for all potential clinical circumstances. This guideline is not intended to supplant clinician judgment, and its recommendations should not be considered mandates. For all recommendations, we have considered the balance of desirable and undesirable effects, certainty of evidence, patients’ values and preferences, resources required, equity, acceptability, and feasibility. Clinicians are encouraged to apply the recommendations in the clinical context of each individual patient, particularly regarding the patient’s values and preferences.

Methods

Guideline recommendations were developed in accordance with principles outlined by the Institute of Medicine (now the National Academy of Medicine) (4). The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach was used to assess the certainty of evidence and to rate the strength of the recommendations (5–9). Panel composition, conflict-of-interest management, external review, and organizational approval all proceeded in accordance with American Thoracic Society (ATS) policies and procedures (10). The final panel included individuals with documented expertise in guideline methodology, behavioral health, health equity, nursing, pharmacy, and/or pediatrics. One member-in-training and one patient representative were included. Two committee members represented countries outside of North America. All panelists disclosed their potential conflicts of interest to the ATS. Most panelists were determined to have no substantial conflicts of interest and were approved to participate.
Figure 1. Logic model for identification of important clinical questions and translation into evaluable PICO-formatted questions. NRT = nicotine-replacement therapy; PICO = Population, Intervention, Comparator, Outcome.

Questions and Outcomes of Interest

Seven question in the PICO (Population, Intervention, Comparator, and Outcome) format were chosen for inclusion in the guideline (Figure 1). One question was discarded in May 2019 because of an absence of evidence and was replaced with an alternative question (PICO 3), leading to a recommendation based on available evidence. After comparing varenicline, nicotine patches, and bupropion in questions 1 and 2, varenicline was shown to be the best controller of the three; therefore, varenicline replaced the "optimal controller" in questions 3 through 6 when formulating recommendations.

The panel selected and defined outcomes for each question a priori and then rated the importance of each using a 9-point scale (11). The panel identified two critically important outcomes relevant to all questions: 1) abstinence, measured by biomarkers or self-report, for the 7 days before follow-up, performed at least 6 months after the target stop date, and 2) incidence of SAEs. Important outcomes also informed decision-making, including 1) abstinence during the treatment period, 2) tobacco-use relapse, 3) increase or decrease in other substance use, 4) quality of life, 5) severity of withdrawal, and 6) change in tobacco-use patterns.

Literature Search

A medical librarian worked with methodologists to identify available evidence without limits on publication date or language. The initial search was completed in January of 2019 and updated through October of 2019. For detailed search strategies, see online supplement.

Evidence Synthesis

The methodology team followed principles outlined in the Cochrane Handbook for Systematic Reviews of Interventions, using title and abstract screening, full-text screening, and data extractions performed independently and in duplicate (12). For each question, the GRADE “Evidence-to-Decision” framework was used to construct tables summarizing the results of systematic reviews (5, 6, 9).

Relative risks (RRs) were used to report analysis of dichotomous outcomes, mean differences were used for continuous outcomes, and hazard ratios were used for time-to-event outcomes. The absolute risk reduction (ARR) presents the result in terms of the anticipated increase or decrease in patients experiencing the effect per 1,000 patients treated (13). The lead methodologists categorized the certainty in the estimated effects into four degrees ranging from very low to high, as determined by considering the risk of bias, precision, consistency, directness, likelihood of publication bias, presence of a dose–effect relationship, and potential effect of residual and opposing confounding (7, 8, 14). Panel members reviewed the evidence profiles and Evidence-to-Decision tables (see online supplement) and provided feedback on the completeness of the data set.

Recommendations were formulated after panel members evaluated the benefits and harms, certainty in the estimated effects, assumptions about values and preferences, resource use, feasibility, acceptability, and
Box 1. Foundations of Tobacco Dependence Treatment:

1. All patients should be screened for tobacco use, and the potential diagnosis of tobacco dependence should be assessed.
2. The diagnosis of tobacco dependence, as well as the toxic effects of tobacco exposure, should be incorporated into the patient’s problem list.
3. Simply encouraging patients to stop smoking is insufficient. All patients who use tobacco should be provided with evidence-based treatment, including pharmacotherapy, to help them stop.
4. Tobacco-dependence interventions require longitudinal follow-up, akin to the longitudinal evaluation and management of other chronic illnesses.

Based on longitudinal evaluation and management of other chronic illnesses.

Recommendations

PICO 1: Varenicline or Patch

To begin establishing an “optimal controller” medication, the panel first evaluated the relative effectiveness of a nicotine patch and varenicline. Our systematic review identified 14 randomized controlled trials (RCTs) directly comparing the efficacy of varenicline with that of a nicotine patch. Eleven RCTs reported exhaled carbon monoxide–verified abstinence at 6 months after treatment, and nine reported abstinence during the 10- to 12-week treatment period (11, 16–22). Compared with a nicotine patch, varenicline increased both long-term abstinence (RR, 1.20; 95% CI, 1.09–1.32; ARR, 40 more per 1,000 patients) and abstinence during the treatment period (RR, 1.40; 95% CI, 1.31–1.49; ARR, 101 more per 1,000 patients) (11, 16–24). Varenicline also likely reduced the risk of SAEs compared with the patch (RR, 0.72; 95% CI, 0.52–1.00; ARR, 3 fewer per 1,000 patients) (11, 16, 18, 19, 21–23, 25, 26). Certainty in the estimated effects was high for both 6-month and treatment-period abstinence, whereas it was moderate for SAE estimated effects because of serious imprecision.

The panel concluded 1) that varenicline is superior in achieving long-term abstinence when compared with a nicotine patch and 2) that varenicline is associated with fewer SAEs than a nicotine patch. On balance, the panel concluded that the clinical superiority of varenicline (balance of effect) outweighs its higher price and the possibly important uncertainty or variability of patients’ values and preferences. The panel made a strong recommendation to use varenicline over a nicotine patch. Remarks: To promote adherence to pharmacologic therapy, providers should be prepared to counsel patients about the relative safety and efficacy of varenicline treatment compared with a nicotine patch.

PICO 2: Varenicline or Bupropion

Identifying an optimal controller next required evaluating the relative effectiveness of varenicline and bupropion. Our systematic review identified seven RCTs comparing varenicline with bupropion; four (n = 5,626) evaluated abstinence at 6-month follow-up (16, 27–29) and five (n = 5,655) evaluated abstinence during treatment (16, 27–30). Varenicline increased abstinence at 6-month follow-up (RR, 1.30; 95% CI, 1.19–1.42; ARR, 77 more per 1,000 patients) and during active treatment (RR, 1.41; 95% CI, 1.32–1.52; ARR, 147 more per 1,000 patients) while probably reducing the risk of SAEs compared with bupropion (RR, 0.81; 95% CI, 0.57–1.16; ARR, 3 fewer per 1,000 patients). Certainty in the estimated effects was high for 6-month and active treatment abstinence but was moderate for SAEs because of imprecision.

The panel concluded 1) that varenicline showed a large, desirable effect in achieving abstinence compared with bupropion, with high-certainty evidence, and 2) that varenicline treatment likely results in little to no difference in SAEs compared with bupropion. On balance, the panel concluded that the clinical superiority (balance of effect) of varenicline outweighs its higher price and the possibly important uncertainty or variability of patients’ values and preferences. As a result, the panel chose to make a strong recommendation to use varenicline over bupropion.

PICO 3: Varenicline plus Patch or Varenicline Alone

Given varenicline’s agonist–antagonist properties, it is commonly held that combining varenicline with nicotine pharmacotherapy should be of limited utility (31). However, nicotine’s effects on the brain are complex and extend beyond the nicotinic receptor system. With varenicline being the optimal controller for initiation, it became important to evaluate whether supplementing varenicline with nicotine-replacement therapy would be better than using varenicline alone. Our review identified three treatment trials that directly compared varenicline combined with a nicotine patch to varenicline alone, two of which (n = 776) reported on smoking abstinence at 6 months (32, 33) and three (n = 893) of which compared adverse events (32–34). Varenicline plus a nicotine patch significantly increased 6-month (RR, 1.36; 95% CI, 1.07–1.72; ARR, 105 more per 1,000 patients) and during-treatment (RR, 1.31; 95% CI, 1.11–1.54; ARR, 112 more per 1,000 patients) abstinence compared with varenicline alone. The combination trivially increased SAEs (RR, 1.06; 95% CI, 0.27–4.05; ARR, 1
| PICO 1 | Varenicline | Patch | 1.20 (1.09–1.32) | 40 more/1,000 | 1.40 (1.31–1.49) | 101 more/1,000 | 0.72 (0.52–1.00) | 3 fewer/1,000 | High | Strong: favors intervention |
|---|---|---|---|---|---|---|---|---|---|---|
| PICO 2 | Varenicline | Bupropion | 1.30 (1.19–1.42) | 77 more/1,000 | 1.41 (1.32–1.52) | 147 more/1,000 | 0.81 (0.57–1.16) | 3 fewer/1,000 | High | Strong: favors intervention |
| PICO 3 | Varenicline | Varenicline alone | 1.36 (1.07–1.72) | 105 more/1,000 | 1.31 (1.11–1.54) | 112 more/1,000 | 1.06 (0.27–4.05) | 1 more/1,000 | Low | Conditional: favors intervention |
| PICO 4 | Varenicline | Electronic cigarette | 1.44 (0.75–2.80) | 143 more/1,000 | No estimate | No estimate | No estimate | No estimate | Very low | Conditional: favors intervention |
| PICO 5 | Pretreat | Wait | 2.00 (1.70–2.35) | 173 more/1,000 | 2.49 (2.09–2.98) | 308 more/1,000 | 1.75 (0.98–3.13) | 12 more/1,000 | High | Strong: favors intervention |
| PICO 6 | Varenicline | Patch | 1.31 (1.12–1.53) | 36 more/1,000 | 1.78 (0.78–4.08) | 108 more/1,000 | 0.95 (0.54–1.67) | 1 fewer/1,000 | Moderate | Strong: favors intervention |
| PICO 7 | >12 wk | 12 wk | 1.22 (1.07–1.39) | 53 more/1,000 | N/A | N/A | 1.37 (0.79–2.36) | 3 more/1,000 | Moderate | Strong: favors intervention |

**Definition of abbreviations:** N/A = not available; PICO = Population, Intervention, Comparator, and Outcome.

Numerical data are shown as the relative risk (95% confidence interval) or patients/patients treated. For complete evidence tables, together with results of the Evidence-to-Decision process, see online supplement.

*Seven-day point-prevalence abstinence assessed at 6-month follow-up.
†Estimated number of additional (or fewer) patients achieving outcome with intervention.
‡Seven-day point-prevalence abstinence achieved during treatment period.
§PICO 7 long-term abstinence assessed at 12-month follow-up.
more per 1,000 patients) (32–34). Certainty was high for abstinence during 6-month follow-up and active treatment, whereas it was low for SAE estimates because of very serious imprecision.

The panel concluded 1) that varenicline plus a nicotine patch showed a large desirable effect compared with varenicline alone in smoking abstinence and 2) that varenicline plus a nicotine patch may increase the risk of SAEs only slightly compared with varenicline alone. As a result, the panel chose to make a conditional recommendation in favor of varenicline plus a nicotine patch over varenicline alone.

PICO 4: Varenicline or Electronic Cigarette

Despite the established efficacy of U.S. Food and Drug Administration–approved pharmacologic agents for tobacco dependence, a significant number of clinicians have recommended electronic cigarettes (e-cigarettes) to help their patients stop smoking (35–37). With varenicline as the optimum controller, the panel believed it important to evaluate whether varenicline or e-cigarettes should be used to treat tobacco-dependent adults. Our systematic review identified one conference abstract reporting an RCT and one observational study directly comparing varenicline with e-cigarettes. The trial recruited 54 smokers with a history of acute coronary syndrome and provided insufficient methodologic information to assess certainty (38). The observational study reported 1-year (mean) follow-up of 3,093 individuals attempting to quit smoking, including 156 using varenicline and 200 using e-cigarettes (39). Because of the paucity of direct evidence, the panel also considered indirect evidence. Eleven randomized trials comparing varenicline with nicotine replacement (11, 16–24) and two randomized trials comparing e-cigarettes with nicotine replacement (40, 41) were selected, and a network meta-analysis including 8,830 individuals was performed. The RCT suggested an increase in self-reported abstinence of 14.8% (95% CI, 3.9% to 25.8%), supported by the observational data suggesting a non–statistically significant increase in continuous abstinence at 6-month follow-up (mean difference, +4.6%; 95% CI −1.8% to +11%) compared with e-cigarettes. The indirect evidence suggested varenicline might lead to a non–statistically significant decrease in abstinence at 6-month assessment (RR, 0.85; 95% CI, 0.65 to 1.10; ARR, 42 fewer per 1,000 patients) but might lead to increased abstinence at 3-month assessment (RR, 1.10; 95% CI, 0.73 to 1.60; ARR, 22 more per 1,000 patients). Varenicline might decrease the risk of SAEs compared with e-cigarettes (RR, 0.32; 95% CI, 0.071 to 0.82; ARR, 52 fewer per 1,000 patients). Certainty in direct evidence was very low because of inconsistency and a serious risk of bias, and indirect-evidence certainty was very low because of indirectness, imprecision, and risk of bias.

The panel concluded 1) that varenicline showed an uncertain benefit compared with e-cigarettes in abstinence or relapse and 2) that varenicline might have fewer adverse events than e-cigarettes. As a result, the panel made a conditional recommendation favoring varenicline over e-cigarettes. Remarks: The recommendation’s strength reflects very low certainty in the effects used to derive the recommendation. After our evidence synthesis, new evidence emerged regarding serious adverse effects of e-cigarettes. If these serious adverse effects continue to be reported, the strength of the recommendation should be reevaluated. Note that this recommendation is intended for treatment of tobacco dependence under the supervision of a clinician; it should not be extrapolated to unsupervised treatment or recreational use.

The panel made several important observations related to the generalizability of the indirect comparison of varenicline with e-cigarettes. Significant differences in the way nicotine is used (i.e., common comparator) in studies evaluating varenicline or e-cigarettes likely impact effect estimates. In addition, target outcomes are different, with varenicline outcomes reflecting discontinuation of smoking and e-cigarette outcomes reflecting a delivery substitution. E-cigarettes appear to carry their own unique risk profile, with wide variability in effects across product categories, aerosol constituents, ages of initiation, and consumer use patterns (42). The panel, aware of large epidemiologic studies of the respiratory and cardiovascular impact of e-cigarette use, emphasized that the overall health consequences of e-cigarette use have become increasingly suspect (43–45); conversely, the initial safety concerns over varenicline have diminished (46, 47).

Although there was unanimity among the panel regarding the preferred intervention, four panelists (H.J.F., P.G., S. Pakhale, and M.C.P.) advocated for a strong, rather than conditional, recommendation. They were concerned about the safety and effectiveness of e-cigarettes because of case reports that were not included in the evidence synthesis. They cited reports of deaths or disability due to e-cigarette– or vaping-associated lung injury (48–51), burns due to product explosion, acute nicotine poisoning, and seizures, as well as histopathologic injuries in laboratory studies. They noted that such concerns have prompted warnings about e-cigarettes from numerous organizations, each recommending that clinicians rely on medications approved by the U.S. Food and Drug Administration or other regulatory agencies instead of relying on alternative modalities that lack an established evidentiary base (48, 52–55). Two nonvoting panelists later joined the dissent (P.F. and T.L.), but these panelists were unavailable to participate in the panel discussions of the evidence or the formulation and grading of the recommendation.

In August 2019, the CDC issued a Health Advisory based on a collection of cases of severe lung injury related to the use of e-cigarettes (48). Since then, the number of reported cases of vaping-associated pulmonary injury has risen precipitously, and these cases have resulted in a number of deaths (49–51). The panel carefully reviewed the recognized GRADE circumstances in which low-certainty evidence could be used to inform a strong recommendation and concluded that although the syndrome is dramatic in its presentation and tragic in its consequences, the nature of the evidence precluded upgrading the recommendation to strong at this time (15). This recommendation is based on an effort to compare use of varenicline with use of e-cigarettes exclusively within the context of tobacco-dependence treatment and should not be interpreted as an implicit statement of the relative value of e-cigarettes for public health.

PICO 5: Pretreat or Wait for “Ready”

The idea that “readiness to quit” should be assessed has been prominent in tobacco
treatment strategies because of near-universal initial acceptance of the transtheoretical model of behavior change (56). More recently, the relevance of the model has come into question on the basis of observations of the dynamic nature of behavior change (57). Although patients may not be ready to abstain, they may be willing to try tobacco-dependence treatment (58). The panel posed a question evaluating the relative effect of initiating optimal controller therapy before patients express a readiness to abstain. Our systematic review identified four RCTs addressing efficacy of treatment initiation in smokers unready to abstain (i.e., “pretreatment”) (59–62) and identified a fifth evaluating the 15-day experimental effect of varenicline in non–treatment-seeking smokers (63). Self-reported abstinence was biochemically confirmed with exhaled carbon monoxide.

More smokers were able to stop smoking when treated with varenicline, despite initial reluctance. Abstinence at 6-month follow-up (RR, 2.00; 95% CI, 1.70–2.35; ARR, 173 more per 1,000 patients) and 24-week follow-up (RR, 2.49; 95% CI, 2.09–2.98; ARR, 308 more per 1,000 patients) increased with varenicline compared with waiting for affirmation of readiness. Varenicline likely increased SAEs (RR, 1.75; 95% CI, 1.98–3.13; ARR, 12 more per 1,000 patients). Certainty in estimates was high for abstinence at both points and was moderate for SAEs because of imprecision. The evidence suggests varenicline pretreatment would be acceptable to stakeholders (64–67). In addition, the panel considered varenicline pretreatment to be more clinically feasible than asking patients to quit immediately.

The panel concluded 1) that the initiation of varenicline treatment in smokers not ready to abstain showed a large effect on abstinence, with high-certainty evidence, and 2) that initiation of pretreatment showed a small increase in SAEs, with moderate-certainty evidence. As a result, the panel concluded that the clinical superiority (balance of effect) of varenicline in smokers not ready to abstain outweighs its higher price and the possibly important uncertainty or variability of patients’ values and preferences. The panel chose to make a strong recommendation in favor of beginning varenicline treatment in patients who are not ready to quit, rather than waiting for affirmation of readiness. Of note, the panel recognized a potential threat to patient autonomy if the proactive approach is misapplied, whereas autonomy is preserved when patients are engaged in discussion regarding initiating pharmacotherapy with continued smoking and their right to decline treatment is respected.

**PICO 6: Varenicline or Patch in Behavioral Health Patients**

Early black-boxed warnings regarding possible neuropsychiatric adverse effects of varenicline and bupropion limited uptake, despite stemming from case reports and postmarketing surveillance. No early RCT found evidence for these events. In light of persistent stigma assigned to varenicline within the behavioral health community, the panel believed it important to evaluate the evidence guiding the clinical question of whether varenicline or nicotine should be used in adults with comorbid psychiatric conditions (68). Our systematic review identified two RCTs (n = 2,194) directly comparing varenicline with the nicotine patch in a cohort of participants with mental illness (16, 23). Both studies assessed abstinence at 6-month follow-up, abstinence during treatment, and SAE rates. Compared with a nicotine patch, varenicline increased abstinence at 6-month follow-up (RR, 1.31; 95% CI, 1.12–1.53; ARR, 36 more per 1,000 patients) and likely increased abstinence at the end of 12-week treatment (RR, 1.78; 95% CI, 0.78–4.08; ARR, 108 more per 1,000 patients) while probably also decreasing the risk of SAEs (RR, 0.95; 95% CI, 0.54–1.67; ARR, 1 fewer per 1,000 patients). There was one RCT that evaluated the impact of varenicline on use of other substances, which was judged to be unclear because of very low certainty in the evidence (alcohol: RR, 0.56; 95% CI, 0.24–1.3; ARR, 128 fewer per 1,000 patients; other substances: RR, 1.42; 95% CI, 0.71–2.87; ARR, 108 more per 1,000 patients). Certainty in SAE effects was moderate because of serious imprecision, with 95% CIs that could lead to opposing conclusions. The impact of varenicline on risks of other substance use was judged to be of very low certainty because of a serious risk of bias and very serious imprecision due to the small number of events. The panel considered both interventions to be acceptable to stakeholders and to be increasingly feasible to implement with the boxed warning removed.

Compared with nicotine, the panel concluded that varenicline 1) may result in a large benefit for abstinence and 2) would likely result in little to no difference in SAEs, with both results having moderate certainty in the estimated effects, in patients with substance-use or psychiatric disorders. As a result, the panel concluded that the clinical superiority (balance of effect) of varenicline in patients with substance-use or psychiatric disorders outweighs its higher price and the possibly important uncertainty or variability of patients’ values and preferences. The panel chose to make a strong recommendation in favor of initiating varenicline over the patch in patients with comorbid psychiatric conditions, including substance-use disorder, depression, anxiety, schizophrenia, and/or bipolar disorder.

**PICO 7: Extended or Standard Duration**

Relapse after pharmacologic discontinuation is common (69). Among the various strategies aimed at preventing relapse, an extended duration of treatment has been effective at modifying sustained abstinence rates in some contexts (70). The panel found guidance on treatment duration to be of critical importance, comparing extended therapy (i.e., >12 wk) with standard-duration therapy (8–12 wk). Our systematic review identified 12 studies that directly compared extended with standard-duration controller therapy with varenicline, bupropion, or nicotine (71–81). Eight studies (n = 3,711) provided data for the primary abstinence at 12-month analysis, and five reported SAE data (76, 78, 79, 81). Compared with standard-duration controller therapy, extended-duration therapy probably increased abstinence at 1-year follow-up (RR, 1.22; 95% CI, 1.07–1.39; ARR, 53 more per 1,000 patients) and probably reduced relapse assessed at 12–18 months after initiation of therapy (hazard ratio, 0.43; 95% CI, 0.29–0.64). Compared with standard-duration controller therapy, extended-duration therapy probably increased SAEs slightly (RR, 1.37; 95% CI, 0.79–2.36; ARR, 3 more per 1,000 patients). Certainty in the estimated abstinence at 12 months was moderate because of a serious risk of bias. Certainty in estimated SAE effects was moderate because of serious imprecision. The panel considered extended-duration therapy to be acceptable to stakeholders and feasible to implement.
Discussion

From our 21st-century perspective, clinicians engage tobacco use as the cardinal manifestation of a disturbance in the brain’s molecular-learning mechanisms, extending the treatment team’s responsibility beyond encouraging quitting to include maximizing longitudinal control over the compulsion to smoke. The guideline brings clarity to complex clinical decision-making and addresses several limiting misconceptions, including the value of combination pharmacotherapy, the approach to patients reluctant to stop smoking, and the safety and efficacy of treating vulnerable behavioral health populations. Pragmatically, these 7 recommendations (Box 2) provide straightforward suggestions for individual practice change, amplifying the clinician’s ability to check preventable illness. Ideally, they also represent a new set of practice standards for treatment teams, health systems, and payers.

The main limitation of our guideline is the limited number of recommendations included. Because our objective was to identify a functional, evidence-based pharmacotherapy pathway, we began the process by identifying an optimal controller medication on which to build additional clinical recommendations. By necessity, our guideline could not address all possible pharmacotherapy options.

**Patient Perspective**

In 1967, as a young college freshman, I made the decision to smoke—the worst I ever made. I can tell you from experience that the addiction to smoking is real. Every day is going to be the day to quit, but every moment brings reminders that addiction to cigarettes is stronger than the will to quit. Days, months, and years go by, but the quit date keeps getting pushed further into the future.

All smokers face the possibility of lung cancer, heart disease, and other debilitating illnesses, in addition to the societal stigma that tobacco use carries. It’s not surprising that most smokers really do want to quit. Healthcare professionals have a prominent role to play in tobacco dependence. They have the trust of their patients, and their voices are heard across a vast range of social, economic, and political arenas. By developing effective pathways for treating tobacco dependence, the ATS is taking important steps toward changing the impact tobacco dependence will have on future generations.

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**Box 2. Evidence-based Tobacco Dependence Treatment Recommendations:**

1. In tobacco-dependent adults for whom treatment is being initiated, we recommend using varenicline over a nicotine patch.
2. For tobacco-dependent adults for whom treatment is being initiated, we recommend using varenicline over bupropion.
3. In tobacco-dependent adults for whom treatment is being initiated, we suggest offering varenicline plus a nicotine patch over using varenicline alone.
4. For tobacco-dependent adults for whom treatment is being initiated, we suggest using varenicline over electronic cigarettes.
5. For tobacco-dependent adults with comorbid psychiatric conditions, including substance-use disorder, depression, anxiety, schizophrenia, and/or bipolar disorder, for whom treatment is being initiated, we recommend using varenicline over a nicotine patch.
6. For tobacco-dependent adults with comorbid psychiatric conditions, including substance-use disorder, depression, anxiety, schizophrenia, and/or bipolar disorder, for whom treatment is being initiated, we recommend using varenicline over electronic cigarettes.
7. For tobacco-dependent adults for whom treatment is being initiated, we recommend using extended-duration (>12 wk) controller therapy.

Development details and the evidence base are available at http://www.thoracic.org/statements/.

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References

1. U.S. Department of Health and Human Services. The health consequences of smoking: nicotine addiction. A report of the Surgeon General; Atlanta, GA: U.S. Department of Health and Human Services; Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, CDC; 1988 [accessed 2019 Aug 7]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK44695/.

2. Fiore MC, Bailey WC, Cohen SJ, Dorfman SF, Goldstein MG, Gritz ER, et al.; Smoking Cessation Guideline Panel. Clinical practice guideline: smoking cessation. Rockville, MD: U.S. Department of Health and Human Services, USPHS, Agency for Health Care Policy and Research; 1996.

3. Fiore MC, Jaén CR, Baker TB, Bailey WC, Benowitz N, Curry SJ, et al.; Tobacco Use and Dependence Guideline Panel. Treating tobacco use and dependence: 2000 update: clinical practice guideline. Rockville, MD: USPHS, U.S. Department of Health and Human Services; 2008.

4. Institute of Medicine. Clinical practice guidelines we can trust. Washington, DC: National Academies Press; 2011 [created 2011; accessed 2020 Jun 21]. Available from: https://www.nap.edu/fileadmin/user_upload/Leitlinien/International/IOM_CPG_lang_2011.pdf

5. Alonso-Coello P, Schünemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al.; GRADE Working Group. GRADE Evidence to Decision (EID) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. BMJ 2016; 353:i2016.

6. Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al.; GRADE Working Group. GRADE Evidence to Decision (EID) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. BMJ 2016;353:i2089.

7. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al.; GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64:383–394.

8. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al.; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–926.

9. Schünemann HJ, Mustafa R, Brozek J, Santessio N, Alonso-Coello P, Guyatt G, et al.; GRADE Working Group. GRADE Guidelines: 16. GRADE evidence to decision frameworks for tests in clinical practice and public health. J Clin Epidemiol 2016; 76:89–98.
10. ATS Documents Unit. American Thoracic Society guidelines packet. New York, NY: American Thoracic Society; 2018 [accessed 2019 Sep 30]. Available from: https://www.thoracic.org/statements/document-development/resources/gats/index.pdf

11. Aubin H-J, Breda V, Britton JR, Oncken C, Billing CB Jr, et al. Varenicline versus transdermal nicotine patch for smoking cessation: results from a randomised open-label trial. Thorax 2008;63:717–724.

12. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. Cochrane handbook for systematic reviews of interventions. 2nd ed. Chichester, United Kingdom: John Wiley & Sons; 2019. Available from: http://handbook.cochrane.org/handbook

13. Irwig L, Trevena L, Sweet M. Relative risk, relative and absolute risk reduction, number needed to treat and confidence intervals. In: Smart choices: making sense of health advice. London, United Kingdom: Hammersmith Press; 2008 [accessed 2019 Oct 7]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK363467/

14. Atkins D, Eccles M, Flottorp S, Guyatt GH, Henry D, Hill S, et al.; GRADE Working Group. Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches the GRADE Working Group. BMC Health Serv Res 2004;4:38.

15. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 2009;62:77–87.

16. Anthenelli RM, Benowitz NL, West R, St Aubin L, McRae T, Lawrence D, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. Lancet 2016;387:2507–2520.

17. de Dios MA, Anderson BJ, Stanton C, Audet DA, Stein M. Project impact: a pharmacotherapy pilot trial investigating the abstinence and treatment adherence of Latino light smokers. J Subst Abuse Treat 2012;43:322–330.

18. Baker TB, Piper ME, Stein JH, Smith SS, Bolt DM, Fraser DL, et al. Effects of nicotine patch vs varenicline vs combination nicotine replacement therapy on smoking cessation at 26 weeks: a randomised clinical trial. JAMA 2016;315:371–379.

19. Heydari G, Talischi F, Tafti SF, Masjedi MR. Quitting smoking with varenicline: parallel, randomised efficacy trial in Iran. Int J Tuberc Lung Dis 2012;16:268–272.

20. Lerman C, Schnoll RA, Hawk LW Jr, Cinciripini PM, Robinson JD, Karam-Hage M, Minnix JA, Lam C, Versace F, et al. Varenicline versus nicotine replacement therapy vs varenicline alone for smoking cessation: a randomized controlled trial. JAMA 2008;299:47–55.

21. Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, et al.; Varenicline Phase 3 Study Group. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA 2006;296:56–63.

22. Ioakeimidis N, Vlachopoulos C, Georgakopoulos C, Abdelrasoul M, Skiros N, Kaftis V, et al. Smoking cessation rates with varenicline and electronic cigarettes in relapsed smokers with a history of acute coronary syndrome. Int J Tuberc Lung Dis 2018;1–2.

23. Hajek P, Smith KM, Dhanji AR, McRobbie H. Is a combination of varenicline and nicotine patch more effective in helping smokers quit than varenicline alone? A randomised controlled trial. BMC Med 2013;11:140.

24. Kandra KL, Ranney LM, Lee JGL, Goldstein AO. Physicians’ attitudes and use of E-cigarettes as cessation devices, North Carolina, 2013. PLoS One 2014;9:e103462.

25. Steinberg MB, Giovenco DP, Delorne CD. Patient-physician communication regarding electronic cigarettes. Prev Med Rep 2015;2:96–98.

26. Balsdassari SR, Chupp GL, Leone FT, Warren GW, Tol BA. Practice patterns and perceptions of chest health care providers on electronic cigarette use: an in-depth discussion and report of survey results. J Smok Cessatl 2018;13:72–77.

27. Ioakeimidis N, Vlachopoulos C, Georgakopoulos C, Abdelrasoul M, Skiros N, Kaftis V, et al. Smoking cessation rates with varenicline and electronic cigarettes in relapsed smokers with a history of acute coronary syndrome. Eur Heart J 2018;39:242.

28. Kandra KL, Ranney LM, Lee JGL, Goldstein AO. Physicians’ attitudes and use of E-cigarettes as cessation devices, North Carolina, 2013. PLoS One 2014;9:e103462.

29. Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N, et al. A randomized trial of E-cigarettes versus nicotine-replacement therapy. N Engl J Med 2019;380:629–633.

30. Bullen C, Howie C, Laugesen M, McRobbie H, Parag V, Willman J, et al. Electronic cigarettes for smoking cessation and reduce cigarette consumption? Findings from a nationally representative cohort of American smokers. Am J Epidemiol 2018;187:2397–2404.

31. Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N, et al. A randomized trial of E-cigarettes versus nicotine-replacement therapy. N Engl J Med 2019;380:629–633.

32. Bullen C, Howie C, Laugesen M, McRobbie H, Parag V, Willman J, et al. Electronic cigarettes for smoking cessation and reduce cigarette consumption? Findings from a nationally representative cohort of American smokers. Am J Epidemiol 2018;187:2397–2404.

33. Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N, et al. A randomized trial of E-cigarettes versus nicotine-replacement therapy. N Engl J Med 2019;380:629–633.

34. Bullen C, Howie C, Laugesen M, McRobbie H, Parag V, Willman J, et al. Electronic cigarettes for smoking cessation and reduce cigarette consumption? Findings from a nationally representative cohort of American smokers. Am J Epidemiol 2018;187:2397–2404.

35. Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N, et al. A randomized trial of E-cigarettes versus nicotine-replacement therapy. N Engl J Med 2019;380:629–633.
45. Hedman L, Backman K, Stridsman C, Bosson JA, Lundbäck M, Lindberg A, et al. Association of electronic cigarette use with smoking habits, demographic factors, and respiratory symptoms. BMJ 2012;344:e3856.

46. Prochaska JJ, Hilton JF. Risk of cardiovascular serious adverse events associated with varenicline use for tobacco cessation: systematic review and meta-analysis. BMJ 2012;344:e2856.

47. Kotz D, Viechtbauer W, Simpson C, van Schayck OCP, West R, Sheikh A. Cardiovascular and neuropsychiatric risks of varenicline: a retrospective cohort study. Lancet Respir Med 2015;3:761–768.

48. Office on Smoking and Health. Smoking and tobacco use: electronic cigarettes. Atlanta, GA: CDC; 2019 [accessed 2019 Oct 6]. Available from: https://www.cdc.gov/tobacco/basic_information/e-cigarette/severe-lung-disease.html.

49. Layden JE, Ghinai I, Pray I, Kimball A, Layer M, Tenforde M, et al. Pulmonary illness related to e-cigarette use in Illinois and Wisconsin: final report. N Engl J Med 2020;382:903–916.

50. Perrine CG, Pickens CM, Boehmer TK, King BA, Jones CM, DeSisto CL, et al.; Lung Injury Response Epidemiology/Surveillance Group. Characteristics of a multistate outbreak of lung injury associated with e-cigarette use, or vaping; United States, 2019. MMWR Morb Mortal Wkly Rep 2019;68:860–864.

51. Schier JG, Meiman JG, Layden J, Mikosz CA, VanFrank B, King BA, et al.; CDC 2019 Lung Injury Response Group. Severe pulmonary disease associated with electronic-cigarette-product use: interim guidance. MMWR Morb Mortal Wkly Rep 2019;68:787–790.

52. Bals R, Boyd J, Esposito S, Foronyi R, Hiemstra PS, Jiménez-Ruiz CA, et al. Electronic cigarettes: a task force report from the European Respiratory Society. Eur Respir J 2019;53:1801151.

53. Schraufnagel DE, Blasi F, Drummond MB, Lam DCL, Latif E, Rosen MJ, et al.; Forum of International Respiratory Societies. Electronic cigarettes: a position statement of the forum of international respiratory societies. Am J Respir Crit Care Med 2014;190:611–618.

54. Ibero-Latino-American Respiratory Scientific Societies. Declaration of the Ibero-Latino-American respiratory scientific societies on electronic nicotine delivery systems. Montevideo, Uruguay: Latin American Thoracic Association; 2019 [created 2019 May; accessed 2020 Jun 22]. Available from: https://alatorax.org/es/descargar/adojunto/372-ndcsf-dein-doc-posicion-may-2019-eng.pdf.

55. Brandon TH, Goniewicz ML, Hanna NH, Hatsukami DK, Herbst RS, Robin JA, et al. Electronic nicotine delivery systems: a policy statement from the American Association for Cancer Research and the American Society of Clinical Oncology. J Clin Cancer Res 2015;21:514–525.

56. Prochaska JO, DiClemente CC. Stages and processes of self-change: toward an integrative model of change. J Consult Clin Psychol 1983;51:390–395.

57. West R. Time for a change: putting the transtheoretical (stages of change) model to rest. Addiction 2005;100:1036–1039.

58. Babb S, Malarcher A, Schauer G, Asman K, Jamal A. Quitting smoking cigarettes: a position statement of the forum of international respiratory societies. Montevideo, Uruguay: Latin American Thoracic Association; 2019 [created 2019 May; accessed 2020 Jun 22]. Available from: https://alatorax.org/es/descargar/adojunto/372-ndcsf-dein-doc-posicion-may-2019-eng.pdf.

59. Ebbert JO, Hughes JR, West RJ, Rennard SI, Russ C, McRae TD, et al. Varenicline effects on craving, cue reactivity, and smoking reward. Psychopharmacology (Berl) 2011;218:391–403.

60. Marti J. Assessing preferences for improved smoking cessation medications: a discrete choice experiment. Eur J Health Econ 2012;13:533–548.

61. Aumann I, Treskova M, Hagemann N, von der Schulenburg J-M. Analysis of driving factors of willingness to use and willingness to pay for existing pharmacological smoking cessation aids among young and middle-aged adults in Germany. Appl Health Econ Health Policy 2016;14:441–452.

62. Choo EK, Sullivan AF, LoVecchio F, Perret JN, Camargo CA Jr, Boudreaux ED. Patient preferences for emergency department-initiated tobacco interventions: a multicenter cross-sectional study of current smokers. Addict Sci Clin Pract 2012;7:4.

63. Paterson RW, Boyle KJ, Parmefer CF, Neumann JE, De Civita P. Heterogeneity in preferences for smoking cessation. Health Econ 2008;17:1363–1377.

64. Rogers K. The best drug for quitting smoking can’t shake its suicide stigma. VICE News 2015 Nov 24 [accessed 2019 Oct 9]. Available from: https://www.vice.com/en_us/article/v7gym/the-best-drug-for-quitting-smoking-cant-shake-its-suicide-stigma.

65. Lancaster T, Hajek P, Stead LF, West R, Jarvis MJ. Prevention of relapse after quitting smoking: a systematic review of trials. Arch Intern Med 2006;166:828–835.

66. Schnoll R, Leone F, Veluz-Wilkins A, Miele A, Hole A, Jao NC, et al. A randomized controlled trial of 24 weeks of varenicline for tobacco use among cancer patients: efficacy, safety, and adherence. Psychoneuroendocrinology 2019;106:561–569.

67. Stapleton JA, Russell MA, Feyerabend C, Wiseman SM, Gustavsson G, Sawe U, et al. Dose effects and predictors of outcome in a randomized trial of transdermal nicotine patches in general practice. Addiction 1995;90:31–42.

68. Tønnesen P, Paolletti P, Gustavsson G, Russell MA, Saracci R, Gulsvik A, et al. Higher dosage nicotine patches increase one-year smoking cessation rates: results from the European CEASE trial. Collaborative European Anti-Smoking Evaluation. European Respiratory Society. Eur Respir J 1999;13:238–246.

69. Hays JT, Hurt RD, Rigotti NA, Niaura R, Gonzales D, Durcan MJ, et al. Sustained-release bupropion for pharmacologic relapse prevention after smoking cessation, a randomized, controlled trial. Ann Intern Med 2001;135:423–433.

70. Pomerleau OF, Pomerleau CS, Marks JL, Snedecor SM, Mehringer AM, Namenek Brouwer RJ, et al. Prolonged nicotine patch use in quitters with past abstinance-induced depressed mood. J Subst Abuse Treat 2003;24:13–18.

71. Tennessen P, Neuropsychiatric Dis Treat 2005;1:350–355.

72. Conron IT, Hurt RD, Dakhil SR, Croghan GA, Sloan JA, Novotny PJ, et al. Randomized comparison of a nicotine inhaler and bupropion for smoking cessation and relapse prevention. Mayo Clin Proc 2007;82:186–195.

73. Ebbert JO, Hughes JR, West RJ, Rennard SI, Russ C, McRae TD, et al. Varenicline effects on smoking cessation through smoking reduction: a randomized clinical trial. JAMA 2015;313:687–694.

74. Long-term nicotine replacement therapy: a randomized clinical trial. JAMA 2016;325:183–187.

75. Rennard SI, Finger JR, Talbot SK, Callas PW, Fagerstrom KO. Efficacy of varenicline to prompt quit attempts in smokers not currently trying to quit: a randomized placebo-controlled trial. Nicotine Tob Res 2011;13:955–964.

76. Steinberg ML, Lu S-E, Williams JM. Varenicline for smoking reduction in smokers not yet ready to quit: a double-blind, proof-of-concept randomized clinical trial. Addict Behav 2018;84:20–26.

77. Ebbert JO, Hughes JR, Ring JG, Meta-analysis of varenicline for smoking cessation allowing patients with schizophrenia and bipolar disorder: a randomized clinical trial. JAMA 2014;311:145–154.

78. Schnoll RA, Goetz PM, Veluz-Wilkins A, Blazeckovic S, Powers L, Leone FT, et al. Long-term nicotine replacement therapy: a randomized clinical trial. JAMA Intern Med 2015;175:504–511.

79. Slaim TR, Fiore MC, Smith SS, Fraser D, Bolt DM, Collins LM, et al. Comparative effectiveness of intervention components for producing long-term abstinence from smoking: a factorial screening experiment. Addiction 2016;111:142–155.