Clinical utility of varenicline for smokers with medical and psychiatric comorbidity

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Abstract: Chronic obstructive pulmonary disease (COPD) is a costly and deadly disease afflicting an estimated 210 million people and accounting for 5% of all global deaths. Exposure to cigarette smoke is the greatest risk factor for COPD in the developed world. Smoking cessation improves respiratory symptoms and lung function and reduces mortality among patients with COPD. Cigarette smokers with COPD and other co-morbid conditions such as cardiovascular disease and psychiatric illnesses should receive comprehensive tobacco treatment interventions incorporating efficacious pharmacotherapies. Varenicline, an $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist, is the newest and most effective drug currently available to promote smoking cessation. In conjunction with behavioral interventions and clinical monitoring for potential side effects, varenicline offers great hope for reducing smoking-attributable death and disability.

Keywords: smoking cessation, chronic obstructive pulmonary disease, varenicline

Epidemiology of COPD

Chronic obstructive pulmonary disease (COPD) is a costly and deadly disease. In the United States alone, the disease is responsible for US$42.6 billion in annual expenditures.¹ According to the World Health Organization (WHO), 210 million people around the world have COPD, with approximately 40% of those individuals having moderate to severe disease. Each year, 3 million people die from COPD making it responsible for nearly 5% of all global deaths. By 2030, COPD is predicted to become the third leading cause of deaths worldwide.² In low income countries, indoor air pollution from cooking and heating fuels is the leading cause of COPD. Among middle and high income countries, cigarette smoking is the most important risk factor.²-⁵

Observational data from a number of large studies provides a clear picture of the impact of cigarette smoking on COPD incidence. A large Dutch cohort of 40 to 65 year-old cigarette smokers observed a 8.3% 5-year incidence for moderate COPD.⁶ A large Swedish cohort study among middle-aged and elderly patients with respiratory symptoms estimated a 10-year incidence of 13.5% for the development of COPD.⁷ Another study found that one-half of all continuing smokers developed COPD by age 77.⁸

COPD management

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary provides guidelines for the diagnosis of COPD (FEV₁/FVC < 70%)
and for classification of patients by disease progression (eg, 50% ≤ FEV₁ < 80% of predicted defines moderate COPD). The 2008 GOLD Workshop summary defines four stages of COPD ranging from mild (Stage I) to very severe (Stage IV). Current standard of care for management of patients with COPD is based upon stage of disease and follows the recommendations of the GOLD Workshop (Table 1). Of all the currently available treatment options for COPD, smoking cessation has the most profound impact on the course and prognosis of this disease.

**Smoking cessation for the management of COPD**

Smoking cessation in subjects with mild to moderate COPD significantly slows disease progression. Smoking cessation is associated with an attenuation of the decline in FEV₁ and a decrease in all-cause and COPD-related mortality. The largest randomized clinical trial evaluating the long-term impact of smoking cessation on COPD was the Lung Health Study (LHS). In this study, 5887 smokers with mild to moderate COPD were randomized to receive: 1) a smoking intervention and bronchodilator; 2) a smoking intervention and placebo; or 3) no intervention (“usual care”) over 5 years. The smoking intervention included an emphatic physician recommendation to quit, group meetings focused on behavior modification, and nicotine gum. After quitting, former smokers participated in a relapse prevention program focused on coping skills. Over the 11 years of follow-up with 4517 of the original LHS participants, decline in lung function among those who continued to smoke was twice that of those who had quit. Specifically, FEV₁ in men who continued to smoke declined by 66.1 mL/year compared to 30.2 mL/year for men who achieved smoking abstinence. Likewise, the decline in FEV₁ among women was 54.2 mL/year for smokers and 21.5 mL/year for those who achieved smoking abstinence.

Respiratory symptoms such as dyspnea, wheezing, chronic...
cough and chronic phlegm production significantly improved in participants who received a smoking intervention ($P < 0.0001$).12 Although less than one-quarter (21.7%) of study subjects in the smoking intervention group achieved smoking abstinence at the end of the 5-year study (compared to 5.4% in usual care) all-cause mortality at 14½-year follow-up was significantly lower among participants who received a smoking intervention compared to those who did not (8.83 vs 10.38 deaths per 1,000 person-years; $P = 0.03$). Mortality due to non cancerous respiratory disease was significantly lower in the smoking intervention group than in usual care (0.56 vs 1.08 deaths per 1000 person-years, $P = 0.01$).13

The findings of the LHS highlight the critical role of smoking cessation in the slowing of COPD disease progression and provides empiric support for the idea that smoking cessation is “the most important therapeutic intervention in patients with COPD.”14 Pulmonary and thoracic societies universally consider smoking cessation a critical and indispensable component of COPD management.15–18 Specifically, the GOLD Workshop has identified smoking cessation as the most significant strategy for COPD risk reduction and recommends that all smokers be offered smoking cessation interventions.4

**Comprehensive treatment for tobacco dependence**

The United States Public Health Service (USPHS) Clinical Practice Guideline *Treating Tobacco Use and Dependence* concluded that strong evidence supported the use of both behavioral and pharmacotherapeutic interventions for increasing tobacco abstinence rates. The USPHS recommended the use of two types of behavioral counseling which have been consistently shown to increase smoking abstinence rates: (1) providing practical counseling such as problem-solving, and skills training; (2) providing support during a smoker’s direct contact with a clinician.19

Tobacco dependence is best managed by treating it as a chronic disease: implementing systems to identify all people who smoke, providing brief treatment to all identified smokers, and arranging for more intensive interventions when needed.20,21 As with other chronic problems, relapse is the most likely outcome from any single treatment intervention. While some smokers may achieve long-term smoking abstinence (>6 months) after a single attempt, many others will try to quit multiple times and repeatedly relapse.22,23 Re-engagement of patients in the quitting process is critical. Medication adjustments and behavioral support should be provided until long-term abstinence is achieved. Frequent screening at follow-up visits and the offering of new medications can build confidence and reengage patients in treatment.

**Identifying tobacco users**

Establishing a systematic process to identify all tobacco users is critical. To increase the likelihood of addressing tobacco use, clinicians should have tobacco use status information available before they walk in the examination room. Providing advice to quit smoking increases success, and patients who are advised to quit report higher satisfaction with clinical encounters. Although many patients are asked about smoking and advised to quit, few patients receive assistance or referral to quit.24

**Starting the conversation**

Communicating about smoking during a health care visit can be challenging for providers and difficult for patients. Most general practitioners acknowledge that counseling smokers to quit is important and can be effective. However, providers are frequently concerned that their interventions may negatively impact patient satisfaction despite evidence to the contrary.25 In addition, providers may have a limited repertoire of counseling skills for addressing tobacco use with patients. Qualitative studies have found that there is a tendency by general practitioners to have discussions about stopping smoking only with patients who are motivated or to limit the discussions to health problems caused by smoking.26

Most smokers are ambivalent about stopping smoking despite knowing that smoking causes health problems. Many factors conflict with the desire to stop smoking. Patients anticipate the enjoyment from cigarettes that has been strongly paired with situations and stimuli that are present throughout their day-to-day activities. Withdrawal can be quite painful and relief from withdrawal can be very positively reinforcing. Patients may have concerns about loss of self esteem if a quit attempt fails, concerns about weight gain associated with quitting, and difficulty envisioning how they will manage to “fill the void” once they stop smoking.27 The combination of limited counseling repertoire among providers and the multiple reasons underlying patient ambivalence can decrease the likelihood that patients will talk with their providers about tobacco use and even inhibit patients’ reporting of tobacco related health symptoms.28 However, motivation to stop smoking can quickly change, and people who smoke can be helped to make a quit attempt despite being minimally motivated at first.29,30
Brief interventions adapted from Motivational Interviewing can help to engage a patient in a positive discussion about treatment options or prepare the patient to participate in more intensive treatment.31 One of the main barriers to engaging patients in an in-depth discussion of treatment options may be the difficulty in starting the conversation. A few simple questions can be effective for engaging identified smokers such as: (1) beginning with a non-judgmental open-ended question, (2) eliciting the patient’s self-perceived importance and confidence for stopping, and (3) assessing past quit attempts and treatment.32,33

A useful opening question is “What are your thoughts and feelings about stopping smoking?” This can assure the patient that the physician is interested in the patient’s perspective and provide useful information about a patient’s self-assessed obstacles to and benefits expected from quitting smoking. The motivation to stop smoking is a function of the self-assessed importance a patient places on quitting as well as their self-efficacy for succeeding. Scaling for importance and confidence can be used to elicit and strengthen a patient’s motivation to make a quit attempt and can be a function of the self-assessed importance placed upon quitting, and/or how successful the patient believes they will be if they try to quit. To assess both domains, providers can ask the following “scaling questions”: “On a scale of 0 to 10, with 0 being not important at all, how important it is for you to stop smoking?” and “On a scale of 0 to 10, with 0 being not being not confident at all, how confident are you in your ability to stop smoking?” The provider can then follow-up by asking the patient to elaborate from his or her perspective on why it is important to quit, and share what makes them feel confident they can succeed. The provider can then join the patient to discuss options for enhancing confidence by building future success on past success. Deciding on a plan of therapy can be facilitated by asking “What has helped you in the past to stop smoking for even brief periods of time?” If a patient is willing to make a quit attempt, sufficient treatment intensity should be applied to maximize the likelihood of success.

Incorporating behavioral counseling

A dose-response relationship exists between counseling time and tobacco dependence treatment outcomes.34 Many hospitals, health departments and health care facilities have hired or trained tobacco treatment specialists (TTS). More allied health professionals are becoming certified as tobacco treatment specialists (attud.org).35 and standards for providing evidence-based treatment are becoming recognized. TTS provide assurance to the referring clinician that the tobacco use intervention is consistent with evidence-based guidelines.

If a provider does not have local evidence-based tobacco treatment programs at his or her disposal, a telephone quitline can provide support. Each state in the United States, provinces in Canada, and jurisdictions in many other countries provide tobacco treatment counseling via the telephone. The simplest way for practitioners in the United States to engage patients in the tobacco quitline is to tell patients to call 1-800-QUITNOW after leaving the office. Through the National Network of Tobacco Cessation Quitlines, callers will be routed to the tobacco quitline in their state. States have differing levels of support that they can provide, and patients can receive this information when they call. Practitioners can also learn about the state-specific service offerings through the National Quitline Consortium website (naquitline.org).36 The Internet may also be effective in providing support to patients who are trying to quit smoking. A number of web sites have been developed to support quit attempts such as the American Legacy website “Become an Ex” (becomeanex.org) and Quitnet (quitnet.com). The US National Cancer Institute publishes “Clearing the Air,” a comprehensive guide to quitting smoking that is designed specifically for patient use. Smokers can order a free print copy of the guide or view it online (smokefree.gov).

Pharmacotherapy

Seven “first-line” pharmacotherapies are currently available for facilitating smoking cessation: five nicotine replacement therapies (ie patch, gum, lozenge, inhaler and nasal spray), bupropion sustained-release (SR) and varenicline. Clonidine and nortriptyline have been identified as “second-line” medications.19 “First-line” medications should be selected initially because of their well-reported efficacies and favorable side effect profiles.

All of the available pharmacotherapies indicated for the treatment of smoking cessation have been shown to be effective as monotherapy and are often used as such for light smokers (≤10 cigarettes per day). Our general approach at the Mayo Nicotine Dependence Center for moderate and heavy smokers (>10 cigarettes per day) is to prescribe the nicotine patch to provide continuous dosing and the ad libitum nicotine replacement products (ie nicotine gum, nicotine nasal spray, nicotine inhaler, nicotine lozenge) to cover sudden urges and cravings. As a rough guide, the required patch dose (in milligrams) should be the same or slightly more than the number of cigarettes per day (cpd) smoked.
For example, patients who smoke 30 cigarettes per day could be started on a nicotine patch dose of 35 mg/day (21 mg + 14 mg patches). We offer bupropion SR concomitantly if there are no contraindications. While combination therapy with multiple nicotine replacement therapies is not an FDA-approved treatment strategy, available evidence suggests that combination therapy increases smoking abstinence rates over monotherapy.\(^{37-40}\)

Varenicline is appropriate for patients who have never tried any pharmacotherapy for smoking cessation and for those who have relapsed from abstinence using other medications. The recommended dosing for varenicline is 0.5 mg once daily for three days, twice daily for four days, then 1 mg twice daily for 11 weeks. Starter packs for the first month of therapy with the “ramp-up” are available in some locations. Patients should plan to quit on day 8 (Target Quit Day) of therapy, the point at which the target dose of varenicline is reached. We continue varenicline for 3 months beyond the initial 3 months if patients are at a self-identified risk for relapse.\(^{41}\)

**Interventions for smokers with comorbid COPD**

Tobacco use interventions in patients with COPD have been demonstrated to be effective for increasing smoking abstinence rates. The LHS demonstrated that a combination of behavioral counseling and nicotine replacement therapy (NRT) was effective for promoting smoking cessation in COPD patients. In an 11-year follow-up of the LHS, 21.9% of participants in the smoking intervention group achieved long-term smoking abstinence compared to 6.0% of participants in the control group (\(P = 0.001\)).\(^{11}\) Several other trials assessing the efficacy of pharmacotherapy for smoking cessation have been conducted in patients with COPD with mixed results. One study evaluated the efficacy of 12 weeks of bupropion SR for smoking cessation among 404 COPD patients. While bupropion SR increased smoking abstinence rates at 26 weeks compared to placebo (prolonged abstinence 16% vs 9%; \(P < 0.05\)) no statistically significant difference in abstinence rates was observed between the two treatment groups at 12 months.\(^{42,43}\) In contrast, in a randomized trial of 370 patients with COPD randomized to NRT (sublingual tablet) or placebo, NRT significantly increased smoking abstinence rates at 12 months compared to placebo (biochemically confirmed 7-day point prevalence smoking abstinence: 17% vs 10%; odds ratio [OR]: 1.97; 95% CI: 1.06 to 3.67).\(^{44}\) In a study evaluating the comparative efficacy of bupropion SR and nortriptyline for smoking cessation, 255 subjects with COPD or at risk for COPD were randomized to bupropion SR (150 mg twice daily), nortriptyline (75 mg once daily) or placebo for 12 weeks. Among the subjects with COPD, 26-week prolonged smoking abstinence rates were highest in the bupropion group (27.3% vs 21.2% nortriptyline vs 8.3% placebo).\(^{45}\) The only statistically significant difference in abstinence was between bupropion SR and placebo (\(P = 0.03\)).

**Varenicline for smoking cessation**

Varenicline is the newest addition to the armamentarium of pharmacotherapies for the treatment of tobacco dependence. Varenicline offers new hope to patients with COPD and other co-morbidities attempting to achieve tobacco abstinence.

**Pharmacology of varenicline**

The addictiveness of a drug is directly related to how rapidly it enters the central nervous system, and smoking a cigarette is the quickest way to deliver nicotine to the human body. The addictiveness of nicotine is comparable to heroin, cocaine, and alcohol.\(^{46}\) Nicotine “hijacks” neural networks to produce reward by affecting the release of the dopamine in the mesolimbic system of the brain. Systemically administered nicotine increases extracellular levels of dopamine in the nucleus accumbens\(^{47}\) by acting on nicotinic acetylcholine receptors (nAChRs).\(^{48}\)

Neuronal nAChR receptors are ion channels comprised of \(\alpha\)- and \(\beta\)-subunits.\(^{49}\) Six or more of these subunits (\(\alpha_4, \alpha_5, \alpha_3, \beta_2, \text{ and } \beta_4\)) are expressed in the dopaminergic neurons of the midbrain. The \(\alpha_4 \beta_2\) nAChR in the mesolimbic system plays a critical role in the reinforcing power of nicotine.

Varenicline is an oral medication synthesized from the plant alkaloid cytisine which is known to bind predominantly with high affinity to cerebral \(\alpha_4 \beta_2\) nAChRs.\(^{50}\) Binding at the \(\alpha_4 \beta_2\) nAChRs as a partial agonist,\(^{51,52}\) varenicline stimulates the release of dopamine, which mediates the “reward” reinforcing cigarette smoking while simultaneously blocking the binding of nicotine obtained from tobacco. As a result of this activity, nicotine withdrawal symptoms and cravings are suppressed and reduced pharmacologic reward is experienced if a tobacco-dependent patient smokes a cigarette while taking varenicline.

**Efficacy of varenicline**

Several randomized, placebo-controlled clinical trials have demonstrated the efficacy of varenicline for increasing tobacco abstinence rates among cigarette smokers.\(^{41,53-59}\) Two identically designed clinical trials\(^{55,54}\) compared varenicline...
1 mg twice per day with bupropion SR 150 mg twice per day and placebo. At end-of-treatment (12 weeks), the 7-day point prevalence smoking abstinence rates in both studies were 21% with placebo, 36% with bupropion SR and 50% with varenicline; all pair-wise comparisons within each study were statistically significant \((P < 0.001)\). After 1 year (9 months after treatment had stopped), point prevalence smoking abstinence rates were 28%33 and 31%44 for varenicline and statistically different from placebo \((P < 0.001\) for both studies). Consistent with the proposed mechanism of action, varenicline decreased the urge to smoke, negative affect, and restlessness.53,54

Varenicline also appears to be superior to NRT. In a study of 412 patients, short-term cessation rates (4 weeks after target quit date) were observed to be higher with varenicline than with NRT (adjusted OR 1.70; 95% CI: 1.09 to 2.67).60 In an open-label study of patients randomized to 12 weeks of varenicline or 10 weeks of the 21 mg/day nicotine patch with tapering, the biochemically confirmed continuous abstinence rates (last 4 weeks of treatment) among 746 subjects eligible for analysis were significantly greater with varenicline compared to the nicotine patch (55.9% vs 43.2%; OR 1.70; 95% CI: 1.26 to 2.28).41 Furthermore, varenicline significantly reduced craving, withdrawal, and smoking satisfaction compared to nicotine patch. A systematic review concluded that the pooled relative risk (RR) for continuous smoking abstinence at 1 year for varenicline compared to NRT is 1.31 (95% CI: 1.01 to 1.71).62

In a study investigating the efficacy of an additional 12 weeks of varenicline, point prevalence smoking abstinence rates were higher in the intervention group (6 months of varenicline) compared to control (3 months varenicline + 3 months placebo) at week 24 (OR 2.82; 95% CI: 2.18 to 3.64) and week 52 (OR 1.33; 95% CI: 1.06 to 1.67).41 In a study investigating the long-term (52 weeks) safety of varenicline, the 7-day point prevalence smoking abstinence rate was 36.7% in the varenicline group and 7.9% in placebo. A single serious adverse event in the varenicline-treated group (ie subcapsular cataracts) was observed.55

**Tolerability and safety of varenicline**

The most frequently reported adverse effects of varenicline are nausea (29.4% vs 10% placebo), insomnia (14.3% vs 12.4%), abnormal dreams (13.1% vs 3.5%), headache (12.8% vs 12.6%), and constipation (9% vs 1.5%).54 Nausea is generally mild (72%) to moderate (23%) in intensity, becomes less severe with continued drug use, and causes 2.3% of patients to discontinue treatment. Taking the medication with food can minimize nausea without decreasing the drug’s bioavailability.

Within 2 years of the drug’s approval, the United States Food and Drug Administration (FDA) received reports of agitation, changes in behavior, depressed mood, suicidal ideation, and attempted and completed suicide associated with varenicline use. These symptoms have started days to weeks after initiating therapy and during withdrawal of therapy. In light of these findings, the FDA issued a public health advisory63 for varenicline and advised health care providers to monitor patients for behavior and mood changes.

**Varenicline in smokers with medical comorbidity COPD**

A randomized, double-blind, placebo-controlled multicenter study of varenicline administered for 12 weeks with follow-up through 52 weeks was initiated in 500 subjects with spirometrically confirmed mild to moderate COPD. The study was recently completed; however, the results have not yet been published (clinicaltrials.gov registration number NCT00285012).64

**Cardiovascular disease**

The effect of smoking on the development and progression of coronary heart disease (CHD) is well known, and the benefit of quitting is profound.65,66 The Surgeon General of the United States has named cigarette smoking as the chief preventable cause of CHD and attributed one third of all CHD-related mortalities to smoking, noting that the CHD-related death rate is 70% greater in smokers than in nonsmokers.67,68 In a cohort study on 7735 British, middle-aged men,69 the age-adjusted relative risk for sudden cardiac death (SCD) was related to smoking status. Compared to never smokers, the relative risk for SCD was significantly higher in male current smokers (RR: 2.3; 95% CI: 1.2 to 4.0) and slightly higher among former smokers (RR: 1.4; 95% CI: 0.8 to 2.9).

A high degree of co-morbidity exists between cardiovascular disease (CVD; CVD includes stroke and CHD) and COPD. A population-based study of 20,296 individuals observed that, adjusting for age, sex, smoking, body mass index, race and education, individuals with severe and very severe COPD have an increased risk of CVD (OR 2.4; 95% CI: 1.9 to 3.0).70 Among participants who continued to smoke through the 14.5 year follow-up of the LHS, CVD was the second most common cause of death, and
lung cancer was the leading cause. An estimated 20% of COPD patients ≥65 years of age have undiagnosed comorbid heart failure.

Varenicline appears to be safe and effective for smokers with CHD who wish to quit. The first reported trial of varenicline use in patients with CHD was a multicenter study involving 703 participants aged 35 to 75 years randomized to varenicline (1 mg twice daily) or placebo for twelve weeks along with behavioral support. At 52 weeks, biochemically confirmed prolonged abstinence (4 week grace period) was 19.8% for varenicline and 7.4% for placebo (OR: 3.19; 95% CI: 1.97 to 5.18). The most common adverse events related to the study drug were nausea (29.5%), headache (12.7%) and insomnia (11.9%). Only 2.3% of varenicline-treated subjects discontinued the study medication as compared to 1.4% of subjects in the placebo group. The efficacy reported in this study was similar to previous trials of varenicline for smoking cessation in a general population of cigarette smokers (21.9% vs 8.4% and 23.0% vs 10.3%). No studies directly comparing the efficacy of varenicline with other pharmacotherapies for smoking cessation in patients with CVD have been reported.

**Varenicline in smokers with psychiatric comorbidity**

Because of a higher prevalence of cigarette smoking and a lower likelihood of quitting among individuals with psychiatric illness, these patients are at high risk for developing smoking-related disease. Unfortunately, patients with mental illness are often not included in trials investigating pharmacotherapeutic smoking interventions.

However, the safety and efficacy of varenicline has been evaluated in some studies that included patients with psychiatric illnesses. Within an open-label study on a group of 412 smokers receiving treatment at a tobacco dependence clinic, 111 participants had been diagnosed with psychiatric illnesses. When data from all study participants were pooled, the biochemically confirmed smoking abstinence rates four weeks after the target quit date were higher among patients receiving varenicline than those receiving NRT (72.1% vs 61.3%; adjusted OR: 1.70; 95% CI: 1.09 to 2.67). Varenicline was equally efficacious and not associated with a higher incidence or severity of adverse drug reactions among patients with psychiatric comorbidity. No cases of exacerbations of mental illness were reported. A comparative study on patients with and without a history of depression came to a similar conclusion about the efficacy and safety of the drug in depressed patients.

**Product label warning**

Since the original FDA advisory on psychiatric health concerns related to the use of varenicline was issued in 2008, more reports of psychiatric events possibly related to varenicline have been reported. In response to these mounting reports, the FDA called on Pfizer, the manufacturer of varenicline (branded in the US as Chantix®) to more prominently emphasize concerns about adverse psychiatric potentially associated with the drug. Accordingly, Pfizer sent letters to health care professionals and updated warnings on both patient information sheets and company websites. The new Chantix® product label warning stresses that health care professionals should monitor patients for possible varenicline-induced psychiatric events and encourages patients to discontinue the drug and contact a physician if they experience an adverse psychiatric event.

In a press release by the FDA, Janet Woodcock, director of the agency’s Center for Drug Evaluation and Research, emphasized the need to weigh the risk of adverse events against the benefits of smoking cessation with varenicline. Because the exact relationship between adverse psychiatric events and varenicline is unclear, the FDA concluded that Pfizer will have to conduct a trial to assess the prevalence of psychiatric adverse events in patients taking the drug.

**Conclusions**

Given the health risks associated with smoking and the relationship between smoking status and the progression of COPD and the incidence of CHD, all patients with COPD and CHD who smoke should be offered a comprehensive smoking cessation intervention. Patients with psychiatric illnesses have a higher prevalence of smoking and may have a difficult time quitting. The most effective pharmacologic intervention available is varenicline; however, prescribers should closely monitor patients due to the possibility that the drug may cause psychiatric instability. Behavioral intervention should also be incorporated into every patient’s treatment plan. When face-to-face counseling is not available or feasible, telephone quit lines and self-help guides can offer support for smokers as they make a quit attempt.

**Disclosures**

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