MINDFUL PRACTICE

Is More Better for Smoking Cessation?

BY JON O. EBBERT, M.D., AND ERIC G. TANGALOS, M.D.

The Problem

A 63-year-old man with a history of coronary artery disease, hypertension, and tobacco abuse presents to you for assistance with smoking cessation. He had undergone percutaneous transluminal coronary angioplasty with drug-eluting stent placement for unstable angina 6 months previously. During this hospitalization, he visited with a tobacco dependence counselor, who recommended nicotine patches. He was placed on a tapering regimen with the patch, but within 3 weeks of stopping the regimen, he relapsed because of strong cravings. He tried varenicline 2 years ago but discontinued therapy due to vivid dreams. He is currently on aspirin, metoprolol, and clopidogrel. He is motivated to quit but lacks confidence in his ability to do so. Because of his high risk and previously unsuccessful attempts with pharmacotherapy, you wonder if multiple medications would be better than monotherapy.

The Question

In patients with coronary artery disease, are multiple medications more effective than single-agent therapy for increasing smoking abstinence rates?

The Search

You log on to PubMed (www.pubmed.gov) and enter "drug therapy" AND "smoking cessation" and limit the search to randomized, controlled trials. You find a relevant study. (See box at right.)

Our Critique

This study was well conceived and designed, and stands as a brilliant example of the type of research that needs to be conducted to move the clinical treatment of tobacco dependence forward. The monotherapy intervention resembled what classically occurs in clinical practice and was without inherent flexibility. In contrast, the combination therapy group received a tailored intervention that allowed for a large degree of latitude for individual differences in severity of tobacco dependence and quitting experiences. The generalizability of the combination therapy may be limited because some patients might need higher levels of support and counseling than may be available in some practices.

Clinical Decision

You assess for relative contraindications to the use of bupropion SR, including history of seizures; history of closed head trauma with loss of consciousness for longer than 30 minutes, amnesia, or skull fracture or subdural hematoma/brain contusion; anorexia or bulimia; and use of MAO inhibitors. This patient has none of these contraindications, and he agrees to start triple therapy. Your nurse will call him 2 days after his quit date to assess his status.

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M.B. Steinberg, et al.

Triple-combination pharmacotherapy for medically ill smokers: A randomized trial. Ann. Intern. Med. 2009;150:447-54.

► **Design and Setting:** Randomized, two-arm clinical trial done in the primary care setting.

► **Subjects:** Potential subjects had to be at least 18 years old, smoke an average of at least 10 cigarettes per day, be interested in quitting within the next 30 days, have smoked at least 20 of the past 30 days, and have one or more predefined illnesses including cardiovascular or other vascular disease, chronic obstructive pulmonary disease, cancer, hypertension, diabetes mellitus, hyperlipidemia, or recurrent pulmonary infections.

► **Intervention:** Eligible subjects were randomized to monotherapy with nicotine patch 21 mg/day for 6 weeks, followed by 14 mg/day for 2 weeks and 7 mg/day for 2 weeks (total 10 weeks); or combination therapy with nicotine patch 21 mg/day, a nicotine oral inhaler to be used ad libitum, and bupropion SR (sustained release). Subjects were asked to select a target quit date within 2 weeks of the initial contact. For the combination therapy group, the duration of treatment was symptom-triggered, with patients instructed to continue the medications until they experienced 14 days without nicotine withdrawal symptoms or tobacco cravings. At that point, they were instructed to reduce the nicotine patch dose to 14 mg/day for 2 weeks and then 7 mg/day for 2 weeks. If they were symptom-free, they could discontinue the nicotine patch. During the next 2 weeks, they could discontinue the bupropion SR if they felt comfortable but continue the inhaler as long as they needed.

► **Outcomes:** The primary outcome was 7-day abstinence, which was biochemically confirmed by exhaled carbon monoxide at 26 weeks from the target quit date.

► **Results:** A total of 127 subjects were randomized (64 patch only, 63 combination therapy). Subjects in the combination group used medication for a mean of 89 days, compared with 35 days in the patch-only group. In the combination group, 17% of subjects used at least one of the three medications at 26 weeks. Most subjects used bupropion SR for 2-3 months. At 26 weeks, the abstinence rates were significantly higher in the combination group, compared with the patch-only group (35% vs. 19%; confidence interval, 1%-31%; $P = .04$). Subjects in the combination group had a longer time to relapse than the patch-only group (median 65 days vs. 23 days). No differences in abstinence rates were observed between subjects with different comorbidities.

Varenicline Safe for Depressed Patients

BY KATE JOHNSON

MONTREAL — Despite postmarketing concerns about the psychiatric side effects of varenicline for smoking cessation, the medication appears to be safe in patients who are depressed or at risk for depression, Jennifer B. McClure, Ph.D., reported at the annual meeting of the Society of Behavioral Medicine.

In a subanalysis of the Chronicle Offers Management to Patients With Advanced Signs and Symptoms of Heart Failure (COMPASS-HF) trial, 661 smokers with a baseline history of depression, or a risk of depression, were monitored for mood changes and compared with 516 nondepressed smokers during their 12-week course of varenicline (Chantix) combined with behavioral smoking-cessation counseling (J. Gen. Intern. Med. 2009;24:563-9).

In patients with depression, 'we didn't find an overall difference in their qualitative symptom experience or treatment outcomes.'

"We think that physicians should continue to closely monitor patients who are using varenicline, particularly if they have a psychiatric history," she said.

Although people with a history of depression were more likely than nondepressed people to report side effects with the medication, "we didn't find an overall difference in their qualitative symptom experience or treatment outcomes," said Dr. McClure, who is affiliated with Group Health Center for Health Studies, Seattle.

The study, funded by the National Cancer Institute, was a collaborative effort between Group Health; Free & Clear Inc., Seattle; and SRI International, an independent, nonprofit, research and development organization in Menlo Park, Calif. Medication was provided by Pfizer Inc., manufacturer of varenicline.

Varenicline was approved by the Food and Drug Administration about 3 years ago. It works by blocking nicotinic receptors and thus the rewarding effects of nicotine, while stimulating some dopamine release in order to provide relief from craving and withdrawal, Dr. McClure said.

Shortly after its release to market, the FDA raised concerns that varenicline might be associated with increased neuropsychiatric symptoms, including depressed mood, agitation, suicidal ideation, and behavior—particularly in people with a psychiatric history, she said.

"Unfortunately, due to the nature of the reports to the FDA, we are not able to determine if varenicline itself was the cause of the symptoms reported—it's possible they were due to nicotine withdrawal, substance use, the psychiatric conditions themselves, or some other factors. Unfortunately, subjects with a psychiatric history were excluded from the original efficacy trials."

Research shows that between one- and two-thirds of smokers have a history of depression, and that smokers with a history of depression report more symptoms of nicotine withdrawal, have more negative affect after they quit, and have higher relapse rates, compared with nondepressed smokers, she added.

"But because varenicline does stimulate some release of dopamine, it's possible that it might ameliorate some of this negative effect and other side effects, and so prevent relapse."

At baseline, the subjects in the study were screened briefly for symptoms of depression. "We didn't do an in-depth clinical interview. We just looked for the hallmark symptoms by asking: 'Have you ever, for a 2-week period or more, felt down, depressed, or hopeless, or had little interest or pleasure in doing things?' " she said.

Depressed and nondepressed subjects had similar nonsmoking rates at 21 days (49% vs. 47%, respectively) and 3 months (45% vs. 43%, respectively). However, depressed patients were more likely to report depression, anxiety, tension, agitation, difficulty concentrating and sleeping, and confusion. Depressed patients also were more likely to report other known side effects of the medication. However, despite this, negative affect actually declined in both groups, Dr. McClure said. One case of suicidal ideation was reported in a subject with undisclosed, untreated bipolar disorder.

Additional research is necessary in order to more fully tease out the safety and effectiveness of varenicline among psychologically vulnerable populations, she concluded.

Dr. McClure said she had no conflicts to disclose in connection with this study. ■