

## Invited Commentary

# Improving the Success of Treating Tobacco Smokers

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**Despite decades of progress** in the public health fight to reduce tobacco use, smoking remains the leading preventable cause of death in the United States.<sup>1</sup> For the approximately 40



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million US smokers left, the epidemiological evidence is clear: they will benefit from stopping smoking no matter how long they have smoked.<sup>1</sup> Effective treatments to help smokers quit are available, but patients still struggle to become tobacco free.<sup>2</sup> Most physicians now consider addressing patients' tobacco use to be part of their job, but doing so can be a challenge. How can we change this picture?

At the population level, the outcome of treating any disease can be improved by finding a better treatment or by expanding the reach of treatments that already exist. Both apply to treating smokers. We have effective treatments; however, they are imperfect, and most smokers do not use them when they try to quit. Almost 70% of smokers say that they want to quit smoking; more than half say that they tried to do so in the past year, but only one-third used any tobacco cessation treatment in that attempt.<sup>3</sup> This is a gap that physicians could help bridge. Routine brief advice from a physician increases the chance that a smoker will make a quit attempt.<sup>2</sup> We fall short in ensuring that the smokers making those efforts use the treatments that could help them succeed. We can do this by building team-based systems of care into the routine work flow of office practice rather than relying on the physician's actions alone. Essentially, it means building a chronic disease management model for treating tobacco users.<sup>4</sup>

A second strategy to improve outcomes is to identify better tobacco cessation treatments. The existing treatments improve a smoker's chance of success, but even the best approach—a combination of pharmacotherapy and counseling—typically produces long-term abstinence rates of only 25% to 30% after any single quit attempt.<sup>2</sup> This is better than the estimated 6% success rate of smokers who try to quit without treatment, but it leaves plenty of room for improvement.<sup>3</sup> Despite ongoing efforts to improve treatment, no new smoking cessation aid is nearing US Food and Drug Administration (FDA) approval, to my knowledge. With no new drug on the horizon, research is exploring whether we could improve the effectiveness of our existing medications.

For example, we are still learning how to optimize the dose and delivery of nicotine replacement therapy (NRT), although the first product, nicotine gum, reached the US market in 1988. Manufacturers have since developed new products (patch, lozenge, nasal spray, and oral inhaler) and tweaked their formulations to enhance consumer appeal. Investigators learned that using an individual product often fails to fully suppress a smoker's cigarette cravings or nicotine withdrawal symptoms. They achieved higher quit rates by combining NRT products, specifically by pairing the skin

patch, a long-acting slow-onset product, with a rapid-delivery short-acting product such as the lozenge, gum, inhaler, or nasal spray. The latter product is used as needed for withdrawal symptom control by a smoker wearing the patch. Combination NRT has outperformed single NRT agents in clinical trials and is endorsed in national clinical guidelines.<sup>2</sup> It is a better way to use NRT, and it provides physicians with a new option to offer to smokers who may have already failed with a single NRT product.

Another strategy to improve treatment efficacy is to combine drugs with different mechanisms of action, much as we do in treating hypertension or diabetes mellitus. Two recent studies<sup>5,6</sup> tested the marginal benefit and tolerability of combining varenicline with another active drug, either bupropion hydrochloride or nicotine patch. Both studies found some improvement over varenicline use alone, although replication is warranted. Combining bupropion and NRT has generated equivocal results, but the combination is used clinically when individual products fail.

A common question faced by physicians is what to do when smokers do not respond to the standard dosage of a drug. Should they increase the dose or switch to a different drug? Randomized clinical trial evidence to guide this decision is rarely available. A study<sup>7</sup> in the current issue of *JAMA Internal Medicine* provides this evidence for varenicline, a first-line FDA-approved smoking cessation aid that is a partial agonist at the  $\alpha 4\beta 2$  nicotinic receptor.

Hajek and colleagues<sup>7</sup> asked the following question: if the standard dosage of varenicline does not appear to be working, will increasing the dose improve cessation success and be tolerable to the patient? They answered the question with an ingenious double-blind randomized placebo-controlled clinical trial design. Smokers who wanted to quit started taking varenicline tartrate in the standard way, increasing the dose from 0.5 to 2 mg/d during the first week to minimize nausea, the most common adverse effect. Ten days after beginning varenicline use and well before the target quit date on day 21, smokers were asked if they had noticed any nausea or any of the changes that varenicline users usually experience before quitting (reduced enjoyment of smoking or smoking fewer cigarettes per day). Only those who tolerated the standard dosage but for whom the drug did not appear to have any effect were enrolled in the actual trial. They were randomly assigned to continue the standard dosage or to increase it incrementally before the quit day, reaching a dose of 5 mg/d if tolerated. The drug was taken for an additional 12 weeks after the quit day, and outcomes were measured at that point. Smokers were closely monitored for adverse effects and for nicotine withdrawal symptoms, and they concurrently received a moderate amount of psychosocial support to aid quitting.

The results of the study<sup>7</sup> were clear, if disappointing. Increasing the varenicline dose in apparent nonresponders was

tolerable but failed to increase tobacco abstinence rates. More than half of them were able to reach the highest allowed dosage, but the effect on intermediate markers of response was mixed. The higher dosage produced more nausea and decreased smokers' enjoyment of cigarettes, but it did not reduce nicotine withdrawal symptoms or urges to smoke. Additional analyses showed no relationship between achieving a higher dosage and greater success in quitting smoking.

The study<sup>7</sup> has limitations. It had adequate power to detect a large difference in quit rates, from 60% to 80% at 3 months, but not to detect a smaller but still clinically meaningful difference. However, the results did not suggest even a small effect that a larger trial might have detected. The rate of loss to follow-up was substantial considering that participants had a 12-day run-in period before randomization, but it

was balanced between groups and unlikely to affect results. Overall, this was an excellent study that answered a clinically relevant question about how best to use varenicline. Like all good studies, it raises questions, as well as answering them. Why varenicline use helps some but not all smokers is a question that deserves further study, especially an exploration of potential genetic mechanisms.

In the meantime, when varenicline use fails to help a patient, the physician's first step is to establish that the smoker was taking the drug correctly and received at least some counseling support. If so, trying another FDA-approved smoking cessation medication or a combination of medications makes sense. Above all, it is important for smokers to know that their physicians continue to encourage and support their ongoing efforts to become smoke free.

#### ARTICLE INFORMATION

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