Increasing Varenicline Dose in Smokers Who Do Not Respond to the Standard Dosage
A Randomized Clinical Trial

Peter Hajek, PhD; Hayden McRobbie, MB, ChB, PhD; Katherine Myers Smith, DPsych; Anna Phillips, BSc; Danielle Cornwall, MSc; Al-Rehan Dhanji, MB, BS

**IMPORTANCE** Standard varenicline tartrate dosing was formulated to avoid adverse effects (primarily nausea), but some patients may be underdosed. To our knowledge, no evidence-based guidance exists for physicians considering increasing varenicline dose if there is no response to the standard dosage.

**OBJECTIVE** To determine whether increasing varenicline dose in patients showing no response to the standard dosage improves treatment efficacy.

**DESIGN, SETTING, AND PARTICIPANTS** In a double-blind randomized placebo-controlled trial, 503 smokers attending a stop smoking clinic commenced varenicline use 3 weeks before their target quit date (TQD). Two hundred participants reporting no strong nausea, no clear reduction in smoking enjoyment, and less than 50% reduction in their baseline smoking on day 12 received additional tablets of varenicline or placebo.

**INTERVENTIONS** All participants began standard varenicline tartrate dosing, gradually increasing to 2 mg/d. Dose increases of twice-daily varenicline (0.5 mg) or placebo took place on days 12, 15, and 18 (up to a maximum of 5 mg/d).

**MAIN OUTCOMES AND MEASURES** Participants rated their smoking enjoyment during the prequit period and withdrawal symptoms weekly for the first 4 weeks after the TQD. Continuous validated abstinence rates were assessed at 1, 4, and 12 weeks after the TQD.

**RESULTS** The dose increase reduced smoking enjoyment during the prequit period, with mean (SD) ratings of 1.7 (0.8) for varenicline vs 2.1 (0.7) for placebo (P = .001). It had no effect on the mean (SD) frequency of urges to smoke at 1 week after the TQD, their strength, or the severity of withdrawal symptoms: these ratings for varenicline vs placebo were 2.7 (1.1) vs 2.6 (0.9) (P = .90), 2.6 (1.1) vs 2.8 (1.0) (P = .36), and 1.5 (0.4) vs 1.6 (0.5) (P = .30), respectively. The dose increase also had no effect on smoking cessation rates for varenicline vs placebo at 1 week (37 [37.0%] vs 48 [48.0%], P = .14), 4 weeks (51 [51.0%] vs 59 [59.0%], P = .32), and 12 weeks (26 [26.0%] vs 23 [23.0%], P = .61) after the TQD. There was significantly more nausea (P < .001) and vomiting (P < .001) reported in the varenicline arm than in the placebo arm.

**CONCLUSIONS AND RELEVANCE** Increasing varenicline dose in smokers with low response to the drug had no significant effect on tobacco withdrawal symptoms or smoking cessation. Physicians often consider increasing the medication dose if there is no response to the standard dosage. This approach may not work with varenicline.

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Varenicline tartrate is a partial nicotinic agonist that acts on α4β2 nicotinic receptors. It alleviates withdrawal discomfort but also diminishes rewarding effects of cigarettes smoked if patients lapse when using the drug. Our group previously demonstrated that varenicline used when smoking generates a significant decrease in cigarette enjoyment and smoke intake in approximately 37% of patients. Most important, some patients have no response to varenicline use during the prequit period, and these nonresponders achieve significantly lower quit rates than responders.

It is possible that the correlation between an early response to varenicline use and quitting success is due to the decreased rewards from smoking during the preabstinence period, which facilitates smoking cessation. In patients for whom varenicline use diminishes smoking enjoyment, the drug may also diminish withdrawal discomfort later on, or both factors may have a role. In any case, questions arise as to whether the response to varenicline use is dose dependent and whether nonresponders could become responders with increased likelihood of quitting success by a dose increase.

Standard varenicline tartrate dosing (a gradual increase to 2 mg/d) was formulated to avoid adverse effects (primarily nausea) in sensitive patients. Higher dosing increases the occurrence of nausea but otherwise seems to be safe; indeed, varenicline tartrate doses of up to 10 mg were examined in phase 1 clinical trials. In dose-escalating (≤10 mg) studies of varenicline tartrate, nausea and vomiting were the limiting factors. No adverse effects remained or developed after discontinuation of the drug. Similarly, no new adverse effects other than nausea were observed in a cohort of smokers who received a varenicline tartrate dosage of 3 mg/d. A case report describes a teenager who ingested thirty 0.5-mg tablets of varenicline tartrate. Apart from vomiting, she experienced no other symptoms, and her physical examination after ingestion was unremarkable. Therefore, there are no a priori reasons to expect any safety issues if the varenicline dose is increased in patients not experiencing any drug adverse effects. The present trial is the first study to date to evaluate the hypothesis that increasing varenicline dose in patients showing no response to the standard dosage improves treatment efficacy.

Methods

Objectives

The study was authorized by the United Kingdom Medicines and Healthcare Products Regulatory Agency and by the National Research Ethics Service. Written informed consent was obtained from all participants. The study was designed to determine whether increasing varenicline dose in patients who show no response to the drug improves treatment efficacy in terms of tobacco withdrawal relief and abstinence rates.

Study Setting, Participants, and Procedures

This was a double-blind randomized placebo-controlled trial based in a specialist stop smoking clinic in London, England, conducted from July 2011 to February 2013 (Figure). Smokers seeking treatment were recruited by local advertising. Volunteers were included if they were 18 years or older, were not breastfeeding or pregnant, had provided informed consent, and had no current psychiatric illness, unstable heart disease, or end-stage renal disease.

Participants began varenicline 21 days before their target quit date (TQD). They were asked to smoke ad libitum rather than try to limit their smoking. On day 10 of varenicline use, participants were contacted by phone (phone call 1) to assess eligibility for randomization. Those assessed as varenicline nonresponders (ie, participants reporting no strong nausea, no clear reduction in smoking enjoyment, and less than 50% reduction in their baseline smoking) were asked to attend the clinic on day 12 (randomization visit). Participants were reassessed for eligibility on day 12 and, if eligible, were randomized to receive a bottle of varenicline tartrate (0.5 mg) or placebo tablets to use twice daily in addition to their standard active dose. Ineligible volunteers (varenicline responders) were provided with standard United Kingdom National Health Service treatment, including continued use of varenicline.

Randomized participants were contacted by phone on days 15 and 18 (phone calls 2 and 3) to assess their responses to the increased dose. In those who reported no strong nausea or other adverse effects, the dosage was further increased in increments of 0.5 mg twice daily up to a maximum of 5 mg/d (2 mg from the standard dosage pack plus 3 mg from the post-randomization bottle). The dosage used at the TQD was maintained for 3 weeks, with an option to reduce it if required. Participants started reducing their dose at 3 weeks after the TQD, and only the standard dosage of the commercial supply was used from 4 weeks onward after the TQD.

Participants attended the clinic for their TQD session after 21 days of varenicline use, followed by further weekly support sessions according to a withdrawal-oriented treatment protocol, as provided by the National Health Service Stop Smoking Service. Participants also received a supportive phone call at 24 hours after the TQD. Tablet use, withdrawal symptom ratings, adverse effects, and smoking status were assessed at each session. Participants were also invited to attend a session 12 weeks after the TQD to establish smoking status. Participants received 2 payments of £15 ($23.75) at sessions 1 and 4 weeks after the TQD.

Trial Medication

Commercial supplies of varenicline tartrate were used as per standard labeling (0.5 mg/d for the first 3 days, 1 mg/d on days 4-7, and then 2 mg/d for 11 weeks). Participants received 2-week supplies at screening and randomization and 4-week supplies at 1 and 4 weeks after the TQD.

At randomization, participants received a bottle of varenicline or placebo tablets to use in addition to the commercial supplies during the tailoring period before the TQD. Further bottles of varenicline or placebo tablets were provided on the TQD and at 1 week after the TQD.

Main Outcomes and Measures

Participants rated their smoking enjoyment during the prequit period and withdrawal symptoms weekly for the first 4...
Continuous validated abstinence rates were assessed at 1, 4, and 12 weeks after the TQD.

Demographic details, smoking history, and results of the Fagerström Test for Nicotine Dependence were assessed at session 1. The Mood and Physical Symptoms Scale, which assesses tobacco withdrawal symptoms and urges to smoke, was completed at all contacts. Patients rate how they have been feeling during the past week with regard to depression, irritability, restlessness, hunger, poor concentration, and poor sleep at night on a scale ranging from 1 (not at all) to 5 (extremely). To assess any effect that tailoring varenicline treatment may have on the experience of nausea, we added nausea to the scale. From the TQD onward, the Mood and Physical Symptoms Scale was used to rate “How much of the time have you felt the urge to smoke in the past week?” (on a scale ranging from 1 [not at all] to 5 [all of the time]) and “How strong have the urges been?” (on a scale ranging from 1 [no urges] to 6 [extremely strong]).

One question was used to assess smoking enjoyment during the week before the TQD, with answers ranging from 1 (much less enjoyable than usual) to 5 (much more enjoyable than usual).

The initial response to varenicline use was assessed by 3 indicators, including whether the participants had found their cigarettes much less enjoyable in the past week, whether they had experienced nausea, and whether they had reduced their cigarette consumption by at least 50%. Those who reported a rating of 1 on the enjoyment question (cigarettes were much less enjoyable), reported a rating of 3 or more on the nausea question (somewhat extreme nausea was experienced), or had reduced their cigarette consumption by 50% or more of the baseline smoking rate were not eligible for randomization.
Several variables were assessed at every contact. These included self-reported smoking status, cigarette consumption during the previous week, end-expired carbon monoxide level, and adverse effects.

Randomization and Blinding
Participants were randomized to treatment arms using sequentially numbered prepackaged medication containers prepared by an independent statistician. The authors were unblinded only after the data analysis was completed.

Sample Size
A sample size of 200 was needed to provide 80% power to detect a difference in 4-week abstinence rates between 60% in the placebo arm (the usual quit rate with varenicline at the trial clinic) and 80% in the varenicline arm (a clinically relevant improvement over the standard quit rate). Two-tailed P < .05 was considered significant.

The Mood and Physical Symptoms Scale is sensitive to tobacco withdrawal symptoms and to pharmacological14 and behavioral15 treatment effects. Effective treatments typically generate a difference in ratings during the first week of abstinence of at least 0.7 compared with control procedures (eg, mean [SD], 1.8 [1.0] compared with 2.5 [1.0]). The selected sample size provides 90% power to detect a difference in ratings of 0.5 (P < .05, 2-tailed test).

Data Analysis
Differences between study arms were assessed using analysis of variance for continuously distributed end points and χ² test for categorical end points. The relationship between prequit variables and postquit end points was assessed using regression modeling.

Continuous abstinence at 4 weeks after the TQD was defined as self-report of no smoking (not a puff) from 2 weeks onward after the TQD, validated by end-expired carbon monoxide level (<9 ppm) at all time points when carbon monoxide readings were scheduled (ie, weeks 1-4 after the TQD). If a session was missed, self-reported continuous abstinence and end-expired carbon monoxide level were assessed at the next attendance. We also calculated 12-week sustained abstinence in accord with the Russell Standard16 as self-report of smoking no more than 5 cigarettes since 2 weeks after the TQD, validated by carbon monoxide level readings as above and at 12 weeks. Participants lost to follow-up were considered to be smoking.

Results
Of 503 consenting volunteers who commenced standard varenicline use, 204 (40.6%) were classified as nonresponders. Of these, 200 were randomized to receive additional tablets of varenicline or placebo. The Figure shows the flow of participants through the trial. Enrollment began in July 2011, and 12-week follow-up data collection was completed by February 2013.

Table 1. Baseline Characteristics of Participantsa

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo Add-on</th>
<th>Varenicline Tartrate Add-on</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic, Mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>44.3 (10.8)</td>
<td>47.3 (12.6)</td>
</tr>
<tr>
<td>Cigarette consumption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>during the previous week</td>
<td>20.3 (7.7)</td>
<td>20.8 (9.9)</td>
</tr>
<tr>
<td>Baseline end-expired carbon monoxide level, ppm</td>
<td>22.9 (8.8)</td>
<td>21.8 (8.3)</td>
</tr>
<tr>
<td>Fagerström Test for Nicotine Dependence score</td>
<td>5.6 (2.2)</td>
<td>5.5 (2.4)</td>
</tr>
<tr>
<td>Age when started smoking, y</td>
<td>16.4 (3.8)</td>
<td>16.3 (4.0)</td>
</tr>
</tbody>
</table>

Demographics, No. (%) (n = 100 in each study arm)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo Add-on</th>
<th>Varenicline Tartrate Add-on</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sexb</td>
<td>80 (80.0)</td>
<td>66 (66.0)</td>
</tr>
<tr>
<td>British white race/ethnicity</td>
<td>68 (68.0)</td>
<td>62 (62.0)</td>
</tr>
<tr>
<td>Married</td>
<td>27 (27.0)</td>
<td>28 (28.0)</td>
</tr>
<tr>
<td>Left school by age 16 y</td>
<td>35 (35.0)</td>
<td>38 (38.0)</td>
</tr>
<tr>
<td>Partner smokes</td>
<td>21 (21.0)</td>
<td>20 (20.0)</td>
</tr>
<tr>
<td>In paid employment</td>
<td>76 (76.0)</td>
<td>76 (76.0)</td>
</tr>
</tbody>
</table>

P < .05 was significant. Please note that the number of participants varies because of missing data.

Table 2 lists adverse effects reported after randomization by more than 5% of participants in at least 1 study arm. There was a trend for more reports of fatigue and decreased appetite in the varenicline arm and significantly more reports of nausea and vomiting in the varenicline arm.

Before randomization, there were no differences in smoking enjoyment ratings between the 2 groups. Increased varenicline dose reduced smoking enjoyment throughout the dosing prequit period (Table 3).

Among participants who were abstinent in the first week after the TQD (37 in the varenicline arm vs 48 in the placebo arm), extra varenicline had no effect on the mean (SD) ratings of the frequency of urges to smoke (2.5 [1.1] vs 2.4 [0.8], P = .72) or their strength (2.5 [1.1] vs 2.6 [1.0], P = .53) at 1 week after the TQD. Similarly, there was no significant difference in the mean (SD) ratings for any single withdrawal symptom or in the composite withdrawal score (1.6 [0.4] for varenicline vs 1.6 [0.5] for placebo, P = .67). Including all participants rather than abstainers alone did not change the mean (SD) ratings of the varenicline arm vs the placebo arm for the frequency of urges to smoke (2.7 [1.1] vs 2.6 [0.9], P = .90), their strength (2.6 [1.1] vs 2.8 [1.0], P = .36), or the composite withdrawal score (1.5 [0.4] vs 1.6 [0.5], P = .30).
Continuous validated abstinence rates by end-expired carbon monoxide level are listed in Table 4. There were no significant differences between the 2 study arms at any time point. Controlling for other univariate predictors of abstinence at each time point (cigarette consumption at weeks 1 and 4 and results of the Fagerström Test for Nicotine Dependence at week 4) did not alter outcomes.

eTable 2 in the Supplement lists abstinence rates at the 3 time points among participants who progressed to different dosing. Abstinence rates were similar in participants reaching different dosing.

Nausea ratings were mild but consistently higher in the varenicline arm throughout the increased dosing period (eTable 3 in the Supplement). Before randomization, there were no differences in nausea ratings between the 2 groups at any time point (ratings range, 1.3-1.4 in both groups).

There was no significant correlation between nausea ratings and ratings of change in smoking enjoyment at the time of randomization \( r = -0.09, P = .23 \) (n = 200), but an association emerged at the TQD \( r = -0.26, P = .001 \) (n = 168). Regarding the association of these 2 prequit variables with treatment outcome at 4 weeks, neither variable predicted abstinence, but there was limited variation because smokers with marked nausea or reduction in smoking enjoyment were not included in the study.

### Discussion

Increasing varenicline dose in smokers who showed no response to the standard dosage reduced participants’ smoking enjoyment during the prequit period. It had little effect on tobacco withdrawal ratings after the TQD or on abstinence.

A recent study from Spain described a cohort of smokers who were not fully successful after 8 weeks of standard varenicline dosing (2 mg/d) and received an extra tablet, increasing the dose to 3 mg/d. The success rate of 42% at 6 months was high. However, this observational study could not determine whether results would be different with an extended standard dosage. A hypothesis could be formulated that initiating the drug increase several weeks after the TQD may have better effects than increased dosing early on, but it would seem more logical to expect that a drug targeting withdrawal dis...
comfort would be more beneficial early in the quit attempt when the withdrawal severity is highest.

Increasing varenicline dose before quitting was associated with decreased smoking enjoyment. In a previous study, reduced smoking enjoyment during the prequit period was related to later quit success. In that study, smokers used varenicline for 4 full weeks before quitting. It is possible that the preloading effect of increased varenicline dosing would have had an effect on quit rates if the preloading period had lasted longer. Further studies should test this hypothesis because this approach may be of value with highly dependent treatment-resistant smokers. However, given the high incidence of nausea, this treatment protocol may have limited appeal to patients.

This study included only 3-month outcomes, but results would be unlikely to change with longer follow-up. If an effect was lacking at the short term, when the increased dosing was being used, and at the midterm, including several weeks after the standard dosage had been discontinued, there is no clear mechanism that could make an effect appear several months later.

We conducted several sensitivity subanalyses. Increased dosing had no significant effect on any post-TQD outcome at any single instance or overall. Outcomes in participants who reached different dosing levels showed no sign of any systematic dose response. Sample size could be an issue in studies with negative results, and further studies may be needed to confirm the finding, but we detected no trends for any time point or variable.

The trial evaluated the effect of increased varenicline dosing in nonresponders. It remains possible that increased dosing may enhance abstinence rates in responders, although users who are allowed control over the dosage tend to reduce the dose over time.

Conclusions

The findings herein suggest that the limits to treatment response to varenicline may be due to factors other than insufficient dosage. Above the standard dosage, there may be no further relevant effects on the target nicotinic receptors. Smoking behavior can also have different drivers, and biological differences may exist between smokers in their responses to the drug, with some showing limited response regardless of dosage.

Physicians often consider increasing the medication dose if there is no response to the standard dosage. Our results suggest that this approach may not work with varenicline.

ARTICLE INFORMATION
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Author Contributions: Drs Hajek and McRobbie had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: all authors.
Acquisition, analysis, or interpretation of data: all authors.
Drafting of the manuscript: all authors.
Critical revision of the manuscript for important intellectual content: all authors.
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Additional Contributions: Georgia Knott, MSc, and Anisha Tailor, MSc, both affiliated with Queen Mary University of London, assisted with the conduct of this trial.

Correction: This article was corrected on November 12, 2015, to fix an error in Table 4.

REFERENCES
Improving the Success of Treating Tobacco Smokers

Nancy A. Rigotti, MD

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. For the approximately 40 million US smokers left, the epidemiological evidence is clear: they will benefit from stopping smoking no matter how long they have smoked. Effective treatments to help smokers quit are available, but patients still struggle to become tobacco free. 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. 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. 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 workflow 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.

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. 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. 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. 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 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 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 α4β2 nicotinic receptor.

Hajek and colleagues 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 this 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 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 had 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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Conflict of Interest Disclosures: Dr Rigotti reported receiving royalties from UpToDate, Inc, and reported serving as an unpaid consultant for Pfizer Inc.

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