Efficacy of Varenicline for Smoking Cessation

To the Editor: In their clinical trials of varenicline for smoking cessation, Dr Gonzales and colleagues,[1] Dr Jorenby and colleagues,[2] and Dr Tonstad and colleagues[3] used broad exclusion criteria, particularly for psychiatric disorders of major depressive disorder within the past year; history of or a current panic disorder, psychosis, bipolar disorder, or eating disorder; or alcohol or drug abuse or dependency within the past year. In addition, Tonstad et al[3] excluded potential participants who were taking antidepressants, antipsychotics, or mood stabilizers or anticonvulsants.

However, it is estimated that 30% of smokers have some form of mental illness.[4] Moreover, Lasser et al[5] estimated that persons diagnosed as having a mental disorder within the past month consumed 44% of all cigarettes smoked in the United States. Therefore, the extensive psychiatric exclusion criteria in these trials may make it difficult to apply their results to the general population of smokers. In addition, patients with psychiatric disorders are frequently heavy smokers. Rates of quitting smoking are lower in smokers with psychiatric disorders.[5] Therefore, from a public health perspective, the effect of varenicline also should be assessed in individuals with psychiatric disorders.

Finally, the participants included in the 3 studies examining the effect of varenicline on smoking cessation were not assessed using structured interviews for the diagnosis of psychiatric disorders according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,* or the *International Statistical Classification of Diseases, 10th Revision*. Appropriate instruments include the Diagnostic Interview Schedule and the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Because such instruments are necessary to make an accurate research diagnosis, the study results may have been biased.

Alain Dervaux, MD
a.dervaux@ch-sainte-anne.fr
Mostafa Kanit, MD
Xavier Laqueille, MD
Substance Abuse Treatment Department
Centre Hospitalier Sainte-Anne
Paris, France

Financial Disclosures: None reported.

1. Gonzales D, Rennard SI, Nides M, et al; for the Varenicline Phase 3 Study Group. Varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA*. 2006;296:47-55.
2. Jorenby DE, Hays JT, Rigotti NA, et al; for the Varenicline Phase 3 Study Group. Efficacy of varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA*. 2006;296:56-63.
3. Tonstad S, Tonnesen P, Hajek P, et al; for the Varenicline Phase 3 Study Group. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. *JAMA*. 2006;296:64-71.
4. Leonard S, Adler LE, Benhammou K, et al. Smoking and mental illness. *Pharmacol Biochem Behav*. 2001;70:561-570.
5. Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: a population-based prevalence study. *JAMA*. 2000;284:2606-2610.

In Reply: We are in agreement with Drs Dervaux, Kanit, and Laqueille that all smoking cessation therapies, including varenicline, merit evaluation in population-based effectiveness trials following US Food and Drug Administration approval. These varenicline trials were phase 3 clinical trials designed to investigate safety and efficacy of an investigational drug prior to Food and Drug Administration approval. The exclusion criteria that were specified, including those for psychiatric conditions, were similar to those used in prior studies of investigational drugs for smoking cessation.[1,2] They were chosen for several reasons.

First, investigational drug studies generally exclude participants with poorly controlled medical conditions or use of medications that might compromise either participant safety or evaluation of safety or treatment effects of the drug being studied. Second, because participants in the studies by Gonzales et al[3] and Jorenby et al[4] could have been assigned in a random, double-blind manner to either varenicline, bupropion, or placebo, all participants had to meet safety criteria for the comparator drug (bupropion sustained-release) as well as those for varenicline. As a result, the exclusion criteria regarding psychiatric disorders were designed to be similar to prior bupropion studies.[1,2] Third, the use of the same exclusion criteria used in key bupropion sustained-release smoking cessation trials made possible a more valid scientific comparison between the active treatments. Given that these 3 studies demonstrated efficacy and safety in a healthy population, the next step should be to examine the effectiveness of varenicline in more medically compromised and diverse populations.[5]

Dervaux et al question the assessment of psychiatric disorders in these studies. While self-report was used rather than structured interviews to assess psychiatric history and

GUIDELINES FOR LETTERS. Letters discussing a recent *JAMA* article will have the best chance of acceptance if they are received within 4 weeks of the article's publication date. They should not exceed 400 words of text and 5 references. Letters reporting original research should not exceed 600 words and 6 references. All letters should include a word count. Letters must not duplicate other material published or submitted for publication. Letters will be published at the discretion of the editors and are subject to editing and abridgment. A signed statement for authorship criteria and responsibility, financial disclosure, copyright transfer, and acknowledgment is required for publication. Letters not meeting these specifications are generally not considered. Before submitting a Research Letter, please review the Instructions for Authors (July 5, 2006, or http://www.jama.com). Letters should be submitted via the *JAMA* online submission and review system at http://manuscripts.jama.com (note: do not include "www" before the URL). For technical assistance, please contact jama-letters@jama-archives.org.

Letters Section Editor: Robert M. Golub, MD, Senior Editor.

adverse events, it is likely that the double-blind design of all 3 studies controlled adequately for any potential bias in the study results.

Douglas E. Jorenby, PhD
dej@ctri.medicine.wisc.edu
University of Wisconsin School of Medicine and Public Health
Center for Tobacco Research and Intervention
Madison

Serena Tonstad, MD, PhD
Department of Preventive Cardiology
Ullevål University Hospital
University of Oslo
Oslo, Norway

David Gonzales, PhD
Smoking Cessation Center
Department of Medicine
Oregon Health and Science University
Portland

Financial Disclosures: Dr Jorenby reported receiving research support from Pfizer, Nabi Biopharmaceutical, and Sanofi-Aventis and consulting fees from Nabi Biopharmaceutical. Dr Tonstad reported receiving honoraria for advisory boards and for lectures from Pfizer, GlaxoSmithKline, and Sanofi-Aventis. Dr Gonzales reported receiving research contracts from Pfizer, GlaxoSmithKline, Sanofi-Aventis, and Nabi Biopharmaceuticals; consulting fees and honoraria from Pfizer, Sanofi-Aventis, and GlaxoSmithKline; and owning 5 shares of Pfizer stock.

1. Jorenby DE, Leischow SJ, Nides MA, et al. A controlled trial of sustained release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med*. 1999;340:685-691.
2. Gonzales D, Bjornson W, Durcan MJ, et al. Effects of relapse prevention in smokers treated with bupropion SR. *Am J Prev Med*. 2002;22:234-239.
3. Gonzales D, Rennard SI, Nides M, et al; for the Varenicline Phase 3 Study Group. Varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA*. 2006;296:47-55.
4. Jorenby DE, Hays JT, Rigotti NA, et al; for the Varenicline Phase 3 Study Group. Efficacy of varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA*. 2006;296:56-63.
5. Glasgow RE, Lichtenstein E, Marcus AC. Why don't we see more translation of health promotion research to practice? rethinking the efficacy-to-effectiveness transition. *Am J Public Health*. 2003;93:1261-1267.

Use of Computed Tomography to Assess Coronary Artery Stenosis

To the Editor: In their study of the accuracy of 16-row multidetector computed tomography (MDCT) for assessment of coronary artery stenosis, Dr Garcia and colleagues[1] conclude that MDCT angiography may be useful to exclude coronary artery disease in selected patients in whom a false-positive stress test result is suspected. We have a number of questions about this conclusion and the study.

First, to establish such a role, there must be an assessment of the correlation between clinical pretest probability (55% [132/238] at high risk and 45% [106/238] at intermediate risk), stress test results (abnormal in 117 [74%] of the 158 patients in whom it had been performed), and angiographic outcomes as evaluated by MDCT and quantitative coronary angiography. It would be helpful to know if such an analysis was performed.

Second, the study demonstrated poor accuracy of 16-row MDCT due to a high false-positive rate and a significant false-negative rate. Overall, 143 (60%) of 238 patients could not get a diagnostic scan due to one reason or another. Because of this, it is important to know the average calcium score for true-negative, false-negative, and false-positive results; whether there was a difference between distal and proximal segments; and how the calcium score correlated with diseased segments. Moreover, the false-positivity was attributed in part to the purely quantitative stenosis analysis, and it would be interesting to see a comparison between a blinded qualitative and quantitative segment-based analysis.

Finally, the study enrolled patients from 11 centers, likely with varying ethnic backgrounds. The Multi-Ethnic Study of Atherosclerosis (MESA) study[2] found significant differences in the presence and quantity of coronary calcification by ethnicity that were not explained by coronary risk factors. Therefore, it would be useful to know if there were any differences in calcium scores and disease burden according to race/ethnicity observed in this study, as well as how much interobserver and intraobserver variability there was for the selection of significant lesions.

Abdul Hakeem, MD
a.hakeem@hosp.wisc.edu
Sabha Bhatti, MD
Carrie B. Chapman, MD
Department of Internal Medicine
University of Wisconsin Hospital and Clinics
Madison

Financial Disclosures: None reported.

1. Garcia MJ, Lessick J, Hoffmann MH; CATSCAN Study Investigators. Accuracy of 16-row multidetector computed tomography for the assessment of coronary artery stenosis. *JAMA*. 2006;296:403-411.
2. Bild DE, Detrano R, Peterson D, et al. Ethnic differences in coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*. 2005;111:1313-1320.

In Reply: Drs Hakeem, Bhatti, and Chapman raise several important issues. The primary objective of the Coronary Assessment by Tomographic Scanning and Catheter Angiography (CATSCAN) study was to measure the diagnostic accuracy of 16-row MDCT for the assessment of stenotic coronary artery disease. The study included patients with intermediate or high probability of coronary artery disease who were referred for coronary angiography. The 32% prevalence of obstructive coronary artery disease, defined as at least 1 segment with luminal narrowing of more than 50%, was lower than anticipated, given that all patients had clinical indications for diagnostic catheterization, and 136 (86%) of the 158 patients who had undergone stress testing prior to enrollment had a positive or equivocal result. We are currently performing subgroup analysis to address the utility of MDCT according to stress test results and clinical stratum.

Regarding the overall performance characteristics of 16-row MDCT coronary angiography in our study, the positive predictive value was low (50%) but the negative predictive value was high (99%) in a patient-based analysis for