helped to rule out concomitant silicosis in this case.1 Patients with silicotuberculosis may have resistance to antitubercular medications, and they may need a longer duration of treatment as compared with TB alone;2 hence, it is important to recognize concomitant silicosis in the context of this case report.

Pleuritic chest pain and pericardial effusion on echocardiogram suggest the diagnosis of pericardial TB, but the authors did not mention this in their final diagnosis. Moreover, steroids should have been added for treatment of pericardial TB in addition to standard anti-TB regimen.6

What Justifies a Placebo-Controlled Trial of Varenicline for Smoking Cessation in Patients With COPD?

To the Editor:

In a recent issue of CHEST (March 2011), Tashkin et al1 present results of a double-blind, placebo-controlled, two-arm trial of varenicline for smoking cessation in patients with COPD. The question arises: Why was a trial conducted in which varenicline was compared only with a placebo (and not with another active smoking cessation drug) in this patient group?2

According to article 32 of the World Medical Association’s Ethical Principles for Medical Research Involving Human Subjects, “the effectiveness of a new intervention must be tested against those of the best current proven intervention.”2 The use of a placebo is only acceptable in studies in which no current proven intervention exists. However, nicotine replacement therapy and bupropion were available interventions recommended by international evidence-based guidelines as first-line pharmacologic treatments for smoking cessation in patients with respiratory disease.3 For example, an earlier trial in patients with COPD, notably, conducted by Tashkin et al4 as well, had shown that smokers who received bupropion for smoking cessation achieved higher continuous abstinence rates than smokers treated with placebo. Furthermore, two large-scale trials5,6 had clearly shown the greater benefit of varenicline compared with placebo and bupropion in the general smoking population—1 year before the current trial by Tashkin et al was initiated. The trial by Tashkin et al is the first to investigate the efficacy of varenicline in patients with COPD, but the authors do not provide compelling and scientifically sound methodologic reasons that justify the use of a placebo control instead of existing evidence-based smoking cessation medication. They only state that smokers with COPD have higher levels of nicotine dependence and are “more resistant to smoking cessation interventions” than smokers without COPD, but this is true for other subtypes of smokers as well, for example smokers with a lower socioeconomic background.

Two-arm placebo-controlled trials should no longer be conducted because they do not provide sufficient information on the effectiveness and safety of a new smoking cessation drug in relation to existing drugs. Given the evidence base of available pharmacologic aids for smoking cessation, future trials with varenicline (or other drugs) that provide good reasons for using a placebo as a comparator should at least incorporate a third study arm in which the best alternative pharmacologic treatment of smoking cessation is administered. However, a search of international registers (http://apps.who.int/trialssearch) shows that several trials are still recruiting smokers into two-arm placebo-controlled trials with varenicline (for example trials in patients with depression, schizophrenia, bipolar disorder, and HIV) and trials in smokers receiving alternative dosing schedules and varenicline for relapse prevention. Researchers, medical ethics committees, and regulatory authorities should keep in mind that the health of smokers in a placebo group is at stake. Smokers from the placebo group have a decreased chance of successful quitting, and each unsuccessful attempt increases the risk of smoking-related disease and reduced life expectancy, especially in a vulnerable group like patients with COPD.

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Financial/nonfinancial disclosures: The authors have reported to CHEST that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

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DOI: 10.1378/chest.10-2900

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With regard to our recently published article reporting the results of a randomized, controlled trial on the effects of varenicline on smoking cessation in patients with mild to moderate COPD: a randomized controlled trial. *Chest*. 2011;139(3):591-599.


**Response**

To the Editor:

Very few previous studies of pharmacotherapy for smokers with COPD have been published. In one such study, as noted by Kotz and Schayek, smokers with COPD who had received bupropion achieved significantly higher continuous abstinence rates than smokers treated with placebo at 3 and 6 months, implying that the smokers treated with placebo in the varenicline COPD trial were deprived of an effective pharmacologic aid for smoking cessation as a positive control. However, the bupropion COPD trial, which included a follow-up period up to 1 year, failed to demonstrate a significant difference between bupropion and placebo in continuous abstinence rates at the end of the follow-up period. Consequently, it has not been convincingly demonstrated that bupropion is an effective pharmacologic aid for smoking cessation and sustained abstinence in smokers with COPD. In the absence of evidence that alternative pharmacologic aids for smoking cessation have long-term efficacy in smokers with COPD, we believe that the use of a placebo arm in the varenicline COPD trial (in which all subjects received the benefits of counseling) was justified in order to test the hypothesis that varenicline plus counseling is an effective treatment strategy for promoting long-term abstinence from smoking compared with counseling alone (ie, placebo medication plus counseling).

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**Financial/nonfinancial disclosures:** The authors have reported to the CHEST the following conflicts of interest: Dr Tashkin received grant support from Pfizer Inc and Nabi Pharmaceuticals and fees for attending advisory board meetings from Pfizer Inc. Dr Hays received a research grant from Pfizer Inc for the conduct of the clinical trial described in this manuscript. In the past 3 years, Dr Rennard has been a consultant or a member of an advisory board for AstraZeneca, AstraZeneca, Boehringer Ingelheim, Chiesi, CommonHealth, Consil Complete, COPDForum, Data-Monitor, Decision Resources, Defined Health, Dey, Durr Group, Eaton Associates, Equinox, Gerson, GlaxoSmithKline, Infomed, KOL Connection, M Pankove, MediaCorp, MDRX Financial, Mpx, Novartis, Nymox, Oriel Therapeutics, Otsuka, Pennside Partners, Pfizer Inc (varenicline), Pharma Ventures, Pharmaxis, Price Waterhouse, Propagete, Pulmatrix, Reckner Associates, Recruiting Resources, Roche, Schlesinger Medical, SciMed, Stdler and Hennessey, TargeGen, TheraVance, UBC, Uptake Medical, and VantagePoint Management. Dr Renard has lectured for the American Thoracic Society, AstraZeneca, Boehringer Ingelheim, California Allergy Society, Creative Educational Concept, France Foundation, Information TV, Network for Continuing Education, Novartis, Pfizer, and SOMA and has received industry-sponsored grants from AstraZeneca, Biomarck, Centocor, Mpx, Nabi Pharmaceuticals, Novartis, and Otsuka. Ms Ma is an employee of Pfizer Inc, owns Pfizer stock, and has Pfizer stock options. Dr Lawrence is an employee of Pfizer Inc, owns Pfizer stock, and has Pfizer stock options. Dr Lee is an employee of Pfizer Inc, owns Pfizer stock, and has Pfizer stock options.

**Funding/Support:** This study was funded by Pfizer Inc.

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**References**


