helped to rule out concomitant silicosis in this case. Patients with silicotuberculosis may have resistance to antitubercular medications, and they may need a longer duration of treatment as compared with TB alone; 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.

Alkesh Kumar Khurana, MD, FCCP
Chandigarh, India
Ampu Kumar Singh, MD, FCCP
Rochester, NY

Affiliations: From the Department of Pulmonary Medicine (Dr Khurana), Government Medical College and Hospital; and the Department of Internal Medicine (Dr Singh), Unity Hospital.

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Correspondence to: Alkesh Kumar Khurana, MD, FCCP, Government Medical College and Hospital, Pulmonary Medicine, GMCH Sec 32 Chandigarh, 160030 India; e-mail: lungcancer@rediffmail.com

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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 al presented 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?

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.” 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. For example, an earlier trial in patients with COPD, notably, conducted by Tashkin et al 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 trials 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/trialsearch) 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 smoking 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.

Daniel Kotz, PhD
Onno C. P. van Schayck, PhD
Maastricht, The Netherlands

Affiliations: From the Department of General Practice, CAPHRI School for Public Health and Primary Care, Maastricht University Medical Centre.

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Correspondence to: Daniel Kotz, PhD, Department of General Practice, CAPHRI School for Public Health and Care, Maastricht
Other contributions: We thank Jenny Fidler for her comments on a draft of this letter.

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Response

To the Editor:

With regard to our recently published article reporting the results of a randomized, controlled trial on the effects of varenicline (March 2011),1 Kotz and van Schayck question the justifiability of placebo use as the only comparator in randomized controlled trials of pharmacotherapy for smoking cessation in patients with COPD. They go on to state that “The use of a placebo is only acceptable in studies in which no current proven intervention exists.” What they fail to appreciate is that both the smokers with COPD who were allocated to the placebo and active arms of the varenicline trial received the benefit of counseling for smoking cessation during weekly clinical visits over the 12-week double-blind treatment period and on seven subsequent clinic visits and five telephone visits over the remainder of the 40-week follow-up period. Counseling is effective, and its effectiveness increases with intensity and total amount of counseling according to the US Public Health Service Clinical Practice Guideline on treating tobacco use and dependence.2 Thus, the patients treated with placebo were exposed to a level of counseling for smoking cessation that most likely exceeded that which smokers outside of the study would generally receive.

Very few previous studies of pharmacotherapy for smokers with COPD have been published. In one such study, as noted by Kotz and Schayck, smokers with COPD who had received bupropion achieved significantly higher continuous abstinence rates than smokers treated with placebo at 3 and 6 months,3 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).

Donald P. Tashkin, MD, FCCP
Los Angeles, CA

Stephen Rennard, MD, FCCP
Omaha, NE

J. Taylor Hays, MD
Rochester, MN

Wendy Ma, MS
Shanghai, China

David Laurence, PhD
Theodore C. Lee, MD, FCCP

New York, NY

Affiliations: From the David Geffen School of Medicine at the University of California, Los Angeles (Dr Tashkin); the University of Nebraska Medical Center (Dr Rennard); the Mayo Clinic Nicotine Dependence Center (Dr Hays); and Pfizer Inc (Ms Ma and Drs Laurence and Lee).

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Correspondence to: Donald P. Tashkin, MD, FCCP, Department of Medicine, David Geffen School of Medicine at the University of California, Los Angeles, CA 90095.