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Lung function and respiratory symptoms in a 1-year randomized smoking cessation trial of varenicline in COPD patients

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Summary
There are few data concerning changes in lung function and respiratory symptoms in smokers with chronic obstructive pulmonary disease (COPD) weeks to months after quitting smoking. We examined serial changes in spirometry and Clinical COPD Questionnaire (CCQ) scores (measuring respiratory symptoms and health-related quality of life) in COPD participants by smoking status during a smoking cessation trial.

In this randomized, double-blind trial, smokers with mild-to-moderate COPD were treated with varenicline 1 mg b.i.d. or placebo for 12 weeks and followed to Week 52. Primary endpoints of abstinence were previously reported. Secondary endpoints were mean changes from baseline in post-bronchodilator forced expired volume in 1 s (FEV_1) and CCQ scores.

Change from baseline in post-bronchodilator FEV_1 was significantly improved in continuous abstainers (121.8 mL) *vs.* continuous smokers (37.9 mL) at Week 12 ($P = 0.0069$), but not at Weeks 24 or 52. Mean change from baseline at Week 12 in CCQ Total Score was significantly better in continuous abstainers (−1.04) *vs.* continuous smokers (−0.53; $P < 0.0001$): this improvement was sustained at Weeks 24 and 52.

In a 1-year cessation trial of smokers with COPD, continuous abstinence compared with continuous smoking significantly improved post-bronchodilator FEV_1 at Week 12 (although the difference narrowed subsequently) and CCQ Total Scores at Week 12, with sustained improvement thereafter.

(Trial registry: http://www.clinicaltrials.gov; trial identifier: NCT00285012)

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Introduction

Smoking cessation is the most important strategy for reducing the accelerated rate of decline in lung function[1–3] and for improving respiratory symptoms in smokers with chronic obstructive pulmonary disease (COPD).[4] In the Lung Health Study, as well as slowing age-related decline in forced expired volume in 1 s (FEV_1), smoking cessation was also associated with an absolute improvement in FEV_1 among sustained quitters (participants who were biochemically validated as abstinent at every annual visit) 1 year after enrolment.[2,3] However, there is little information concerning the time course of improvement in lung function or in respiratory symptoms and health-related quality of life (QoL) among COPD patients at earlier time points in the year following smoking cessation. Such information could be useful for informing smokers with COPD regarding how soon the benefits of smoking cessation could be expected after successful quitting.

Since the Lung Health Study demonstrated a significant improvement in lung function and respiratory symptoms in sustained quitters assessed beginning no earlier than 1 year after study entry,[2–4] we examined spirometric indices, as well as respiratory symptoms and health-related QoL, in association with smoking and abstinence at earlier times during the 1-year study period of a randomized, placebo-controlled clinical trial of varenicline—a pharmacotherapy for smoking cessation—in 504 smokers with spirometrically-confirmed mild-to-moderate COPD.[5] Spirometry was administered at baseline and at 12, 24 and 52 weeks following randomization, and a respiratory QoL questionnaire was administered at baseline and regularly during the treatment and follow-up periods. This provided an opportunity to determine the effects of sustained abstinence from smoking on lung function, respiratory symptoms and health status at various times over a 1-year interval following smoking cessation in patients with COPD.

Materials and methods

Participants

Participants were smokers ($\geq$10 cigarettes per day) motivated to quit, with mild-to-moderate COPD (post-bronchodilator FEV_1/forced vital capacity [FVC] $<$70% and FEV_1% predicted $\geq$50%). Participants who used systemic corticosteroids or those who had been treated or hospitalized for a COPD exacerbation during the 4-week period prior to screening were excluded. Other exclusion criteria have been published previously[5] and are listed in Supplemental Table 1. The study was approved by the institutional review board at each site, and participants provided written informed consent. The study was conducted in compliance with the Declaration of Helsinki[6] and the International Conference on Harmonization Good Clinical Practices Guidelines.[7]

Study design

The study was conducted from May 2006 to April 2009.[5] This was a randomized, double-blind, multinational, 27-centre study in which participants with mild-to-moderate COPD received varenicline 1 mg b.i.d. or placebo for 12 weeks (titrated during Week 1), followed by 40 weeks of non-treatment follow-up.[5] Participants were randomized to varenicline or placebo in a 1:1 ratio using a block randomization procedure with investigative site as the stratification variable. Investigators obtained subject randomization numbers and treatment group assignments through a central web-based, or telephone call-in drug management system or through instruction from the sponsor. At the baseline visits, eligible participants received a smoking cessation self-help booklet and $\leq$10 min of counselling. The target quit date (TQD) coincided with the Week 1 visit. Counselling ($\leq$10 min) was provided at clinic visits (weekly from Weeks 1—13, then at Weeks 16, 24, 32, 40, 48 and 52) and by telephone 3 days after the TQD and then in Weeks 14, 20, 28, 36 and 44.

Spirometry was performed before and 30—45 min after the administration of 200 μg albuterol or salbutamol at screening, at baseline and at Weeks 12, 24 and 52, or at early termination visits. Spirometry was performed after any residual bronchodilation from the last dose of COPD medication was expected to have dissipated; participants had been instructed not to take any COPD medication, including inhaled bronchodilators, for the appropriate times before the study visit. Spirometry techniques followed the American Thoracic Society and European Respiratory Society Task Force 2005 Guidelines.[8] The spirometer was required to print the results from at least the three best manoeuvres (numeric results, volume-time graphs and flow-volume graphs). Before any study participants were tested, certification of each study site required evidence of a 3.00 L calibration check demonstrating better than 3% spirometer volume accuracy. The pre- and post-bronchodilator spirometry tests from the first five participant visits were faxed to a central reviewer (P Enright, University of Arizona, Tucson, USA) who graded (A—F) the quality of the FEV_1 and the FVC, as was carried out for the Lung Health Study.[9] Site and technologist certification was awarded when at least 80% of the quality grades were A or B. Whenever possible, the same spirometry technologist tested each participant for the duration of the study. A central review of the quality of the 10 most recent spirometry tests was initiated in June 2008 (around the time of final visits).

At each clinic visit throughout the study, participants completed the Clinical COPD Questionnaire (CCQ; ©2003 Van der Molen et al.),[10] a 10-question instrument using a 6-point Likert scale to assess the symptoms and health status of patients with COPD over the past week.[10] Items on the CCQ are divided into the following domains: Respiratory Symptoms (*e.g.* shortness of breath, cough and phlegm production [4 questions]), Functional State (*e.g.* ability to climb stairs, carry out housework, dress/wash self or visit friends etc. [4 questions]) and Mental State (level of concern about getting a cold or feeling down due to breathing problems [2 questions]) related to their COPD. The Total Score (average of the 10 questions above) can be used to assess the effect of the disease on the QoL of the individual.

Efficacy and safety evaluations

The primary endpoint of the trial was carbon monoxide (CO)-confirmed continuous abstinence rate (CAR) for Weeks