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Authors' reply

We acknowledge the proposition raised by Dr Rose that a comparison of nicotine replacement therapy (NRT) and varenicline using equal pre-cessation treatment regimens may result in different efficacy outcomes from those found in our trial. However, we would like to reiterate that our open-label comparison of varenicline with NRT was a pragmatic trial based on current treatment regimen recommendations by the manufacturers of the products and in accordance with current recommendations for transdermal NRT use in established health guidelines.[1 2]

Dr Rose suggests that the imbalance in pre-cessation treatment between products in our trial reflects a flaw in the design of our study. The objective of this study was to compare a 12-week standard regimen of varenicline with a 10-week standard regimen of transdermal NRT. As the differentiation in treatment between products is openly acknowledged and justified, we would argue that differences in pre-cessation treatment do not reflect a design flaw but, rather, a potential limitation. Even though pre-cessation treatment was not directly referred to, our paper discusses the possibility of a treatment bias resulting from differences in treatment periods between products and recognises this as a limitation of the study.

While use of pre-cessation NRT may be being adopted in some cases, its use is not currently general practice. A standard regimen comparison, as with this open-label design, is therefore more likely to reflect results found in real-world settings. Indeed, recent real-world data from Stop Smoking Services in England provide further support for our findings of greater efficacy with varenicline compared with NRT.[3] The 4-week quit rates in participants set a quit date between April and September 2007 were: varenicline 64% (n = 32 879), bupropion SR 53% (n = 12 767) and NRT 48% (n = 243 123).

The evidence of improved efficacy of transdermal NRT when used during a pre-cessation period in comparison with NRT use without a pre-cessation period[4 5] may provide a rationale for conducting a comparison of varenicline versus NRT with equal pre-cessation treatment periods. The authors of the currently discussed open-label trial agree that this would certainly be an interesting study for future research.

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Competing interests: H-JA has received sponsorship to attend scientific meetings, speaker honoraria and consultancy fees from GlaxoSmithKline, Pierre-Fabre Sante, Sanofi-Aventis, Merck-Lipha and Pfizer. AB has received sponsorship to attend scientific meetings, speaker honoraria and consultancy fees from Boehringer Ingelheim, GlaxoSmithKline, Novartis and Pfizer. In the past 5 years JRB has received consultancy fees from Xenova and Novartis and his employing institution has received consultancy fees and honoraria on his behalf from Pfizer. CO has received honoraria and consulting fees from Pfizer; nicotine and placebo products for research studies at no cost from GlaxoSmithKline; and honoraria from Pri-Med and CME outfitters. CBB, JG, KEW and KRR are employees of Pfizer.

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Clinically significant outcomes in smoking cessation

The study by Aubin *et al*[1] published in this issue comparing varenicline with nicotine replacement therapy (NRT). The authors have shown a significant difference in continuous abstinence rate at the end of treatment of 12 (or 11) weeks, favouring varenicline. However, the beneficial effect is not maintained in a significant fashion up to the end of the study period at 52 weeks. In this context, we would question the validity of measuring abstinence at 12 (or 11) weeks as a primary outcome. It is the long-term outcomes of a smoking cessation therapy that should be most clinically relevant, and therefore the most important finding in this trial. Indeed, the Russell standard recommends that, as a bench mark, quit rates should be assessed at 6 and 12 months and biochemically verified at each point.[2] Other comparative studies using NRT have also used 6- or 12-month periods to assess the efficacy.[3]

Given the fact that there was no significant difference in the abstinence rates at 12 months between the two treatments, it calls into question the cost-effectiveness of varenicline as a pharmacotherapy for smoking cessation. The courses of treatment used in the trial cost £163.80 and £76.31 for varenicline and NRT, respectively.[4] Clinicians are under pressure at all times to cut costs and be evidence-based, and this trial seems to show that there is currently no compelling reason to use the newer, more expensive agent in the smoking cessation clinic, apart from its apparent benefit in reducing craving and some other non-specific effects in the early phases of treatment.

We think the conclusions of the trial are presented in such a way as to give more emphasis to the efficacy of varenicline compared with NRT. But it seems that what this study really tells us is that there is no significant difference in long-term abstinence when comparing varenicline with NRT in an open-label comparison.

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Competing interests: None.

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Authors' reply

We recognise the relevance of showing long-term outcomes of smoking cessation therapies. However, many drug trials use end of treatment measures as primary outcomes.[1 2] Given the high attrition rates during the follow-up phase, choosing long-term primary outcomes has a high impact on the numbers of subjects needed. It is noteworthy that the study cited by Hillman *et al* failed to show any significant difference between the efficacy of a nicotine patch and placebo at 6 and 12 months of follow-up.[3]

We would like to acknowledge that the Russell standard includes six standard criteria.[4] One of these criteria is to use an "intent to treat" approach in which all randomised subjects are included in the analyses (unless they have died or moved to an untraceable address). Using an all-randomised population, our long-term quit

rates are clearly significant, favouring varenicline over nicotine replacement therapy (NRT) ($p = 0.04$).

In addition, while Hillman *et al* question the justification of the additional cost of varenicline over NRT, the NICE technology appraisal guidance concluded that, over a lifetime, varenicline is more cost-effective than both bupropion SR and NRT.[5]

In conclusion, we feel that we honestly reported our results, not claiming any superiority of varenicline over NRT in the long term, either in the abstract or in the conclusion of the paper. Rather, we hoped to convey the message that any intervention shown to be at least as clinically effective as NRT is an important additional option for smokers attempting to quit.

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CORRECTION

doi:10.1136/thorax.57.10.847corr1

G C Donaldson, T A R Seemungal, A Bhowmik, and J A Wedzicha. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002;**57**:847–52.

The legend for fig 2 should read: ''Change in FEV_1 with standard errors over 4 years. Open circles represent frequent exacerbators; closed circles represent infrequent exacerbators.''

Pulmonary puzzle

ANSWER

From the question on page 746

The differential diagnosis for pulmonary infiltrates in the immunocompromised host includes opportunistic infections, drug toxicity, alveolar haemorrhage and progression of the primary disease. The diagnostic yield of bronchoscopy in immunocompromised patients with lung infiltrates is variable with a higher yield (~81%) for infectious aetiologies. On the basis of the larvae in the bronchoalveolar lavage fluid, our case was diagnosed as *Strongyloides* hyperinfection.

Strongyloidiasis is caused by an infection with *Strongyloides stercoralis*, a helminth that can complete its life cycle entirely within the human host.[1] This autoinfection permits the organism to persist for decades and allows hyperinfection to occur in states of impaired cell-mediated immunity.[2] Detection of a large number of larvae in the stool and/or bronchoalveolar lavage fluid or sputum is a hallmark of hyperinfection. The diagnosis requires a high index of suspicion and patients who have peripheral eosinophilia, serpiginous rash or history of soil exposure in tropical and subtropical areas should be screened by stool studies before any form of immunosuppression. In disseminated disease or steroid exposure eosinophilia may be absent.

The respiratory symptoms in strongyloidosis are caused by the migrating larvae producing alveolar haemorrhage, oedema or inflammatory changes. Adult worms are known to cause chronic bronchitis or asthma-like symptoms. The chest radiograph or a CT scan in those with clinical signs and symptoms will usually show abnormal findings including fine miliary nodules or diffuse reticular infiltrates. As the infection progresses there may be bronchopneumonia with scattered ill-defined alveolar, segmental or even lobar opacities similar to those seen in Löffler's syndrome or eosinophilic pneumonitis.

The current treatment of choice for strongyloidiasis is ivermectin with albendazole as an alternative. Our patient was treated with ivermectin for 5 days. He was extubated and his nodular infiltrates cleared slowly over 6 weeks.

Thorax 2008;**63**:753. doi:10.1136/thx.2007.90100a

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