

LETTER TO THE EDITOR

Comment and Reply: *A double-blind study evaluating the long-term safety of varenicline for smoking cessation*

Dear Sir,

Smoking is the leading cause of preventable mortality in the US¹ responsible for over 400 000 deaths annually. Although a number of treatment options exist for smoking cessation¹, the newest drug on the market, varenicline (Chantix, Pfizer) has generated considerable excitement because it has been shown to be more effective than bupropion^{2,3}, and by extension, likely to be more effective than nicotine replacement¹. In earlier studies, varenicline appeared to be safe^{2,3} and to date possesses no known drug–drug interactions. Aside from pregnancy, severe renal dysfunction is its only major precaution⁴, although it also has not been studied in children. These facts increase the enthusiasm for its use.

The recent study by Williams *et al.*⁵ published in the journal reports on longer-term safety and efficacy of this drug when used up to 52 weeks. A total of 251 subjects were randomized to varenicline and 126 to placebo. At week 52, the 7-day point prevalence abstinence rates were 36.7% (varenicline) and 7.9% (placebo).

Unfortunately numerous adverse events emerged on active drug. Over half of the patients dropped out of the study due to an adverse event. Total adverse event rates were 65/251 (25.9%) for patients on varenicline and 13/126 (10.3%) for patients on placebo. This translates into a relative risk of 2.51 for any adverse event causing drop out (95% confidence interval (CI): 1.44–4.38).

Of more concern, serious adverse event also occurred. On active drug, one patient developed bilateral subcapsular cataracts (deemed to be drug related by the investigators, including the investigator who actually examined the patient); and two patients developed coronary artery disease events⁵. Subcapsular cataracts

and heart disease events are listed as side effects on the package insert⁴ but are not discussed by the authors in this study.

Total serious adverse event rates were also greater in the varenicline group than in the placebo group (15/251 vs. 3/126, respectively). This translates into a relative risk of about 2.5 (95% CI: 0.75–8.72). Although this relative risk is not statistically significant, clinically it is quite important in a study that purports drug safety. Further, the authors admit that they do not carry out inferential statistics comparing varenicline with placebo. Nonetheless they proceed to make the inferences that '[v]arenicline 1 mg BID can be *safely* administered for up to 1 year [and] was also a *more effective* smoking cessation aid than placebo throughout the study, *supporting* both its short- (12-week) and long-term (52-week) efficacy' [emphasis added]. Moreover, as listed on clinicaltrials.gov, this study was initiated as a safety trial, yet safety inferential statistics are not available, and, in any case, the study has extremely low power (31%) to detect the differences of serious events seen between varenicline (15/251) and placebo (3/126).

According to the authors, 'Many of [these] serious adverse events were cardiovascular conditions known to be comorbid with cigarette smoking and the medical histories of many of these subjects documented conditions that may have contributed to the events.'⁵ Unfortunately, aside from mentioning the two active-drug cardiovascular (CV) events, the breakdown of other CV events by treatment group is not given, nor is a full list of the all types of serious adverse events.

Oxidative stress is known to play a role both in subcapsular cataract formation⁶ as well as CV disease⁷. Cigarette smoking, in turn, contributes to oxidative stress in both conditions^{6–9}. Thus, diminishing systemic

oxidative stress by smoking cessation is extremely important. In this regard, new and effective pharmacotherapy is always welcomed if the drug is safe.

However, there is the possibility that varenicline itself might instigate oxidative stress. Based on its molecular structure, Kovacic argues in a recent theoretical paper¹⁰ that varenicline can yield an electron transport entity promoting oxidative stress even without extensive metabolism^{10,11}. Additionally, varenicline blocks the alpha-7 nicotinic receptor parasympathetic input to the heart, increasing heart rate; this may also contribute to any putative cardiotoxic effects¹².

In the wake of recent serious, post-marketing adverse events in drugs deemed to be safer alternatives than the drugs they replaced (e.g. rofecoxib¹³), the ocular and CV adverse events seen in this study mandate further analysis. The high level of any adverse event, including other serious adverse events, is also very concerning. Since many of the serious adverse events were cardiovascular in nature, one could possibly conceive that these events would not be reported to the FDA because doctors might assume that the cardiac events were due to the patients being former or current smokers, attributing cardiac events to a patient's smoking history. Until further safety data are available, these concerns should be made broadly public and require a long-term randomized controlled clinical trial adequately powered to determine actual safety.

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Acknowledgment: The author has no potential conflicts of interest to declare in relation to this Letter. Dr Spangler has received past research support from Procter & Gamble and Merck; unrestricted educational support from GlaxoSmithKline; and has served as a paid speaker for Merck, GlaxoSmithKline and Pfizer.

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Authors' reply

Dear Sir,

As noted by Professor Spangler, there is a direct relationship between smoking level and the probability of developing cataracts, with heavy smokers having a three-fold higher risk than non-smokers. This is attributed to tobacco smoke-related reactions in the lens that produce free radicals and consequent oxidative stress. While this risk decreases over time after quitting smoking, it may remain higher than in never smokers even 25 years after quitting¹.

The length limitations of publication manuscripts preclude the inclusion of many details. In the case of the patient who developed subcapsular cataracts in the varenicline long-term treatment study, it is informative to know that this 51-year-old female had a 37-year smoking history of approximately 40 cigarettes per day. Although the subcapsular cataracts were diagnosed on Day 125, she began to experience altered visual acuity on Day 25 at which time she was still smoking (she continued to smoke until at least Day 56). While we acknowledge that the investigator considered this event drug-related (verbatim record 'possibly related'), there is a distinct possibility that the subcapsular cataracts were a result of 37 years of smoking.

It is worth noting also that in a database that comprises 3940 subjects exposed to varenicline in Phase 2/3 clinical trials (cumulatively almost 950 years of exposure), this is the only case of cataracts reported in a subject being dosed with varenicline.

One additional subject who had taken varenicline for 33 days was diagnosed with bilateral posterior subcapsular cataracts 285 days after the last varenicline dose, during the blinded smoking status follow-up period; this event was considered not related to study treatment by the investigator. One case of cataracts was reported for a subject on placebo (among 928 subjects with a cumulative study time of approximately 254 years). A comparison of these incidences indicates that there is no disproportionate occurrence of cataracts in subjects who were treated with varenicline in the clinical trials. This is consistent with expectations founded on the preclinical safety data where, in a whole-body autoradioluminography study in rats conducted to demonstrate distribution of varenicline in the body, no varenicline-associated radioactivity was demonstrated in the lens, cornea, and vitreous body of the eye.

The proposal that varenicline could trigger oxidative stress in the lens and thus cause cataractogenesis is unfounded and speculative; it is based on a hypothesis put forward by Kovacic stating that nicotine causes its addictive effect via an oxidative stress mechanism and that varenicline can also cause oxidative stress. There is no experimental support for these purely hypothetical and highly speculative proposals made by Kovacic in recent publications in *Medical Hypotheses*²⁻⁴. In contrast, there have been no observations of the types of toxicities associated with oxidative stress mechanisms when varenicline was dosed at high doses in laboratory animals. Moreover, if such a hypothesis were true, there would be numerous drugs and other xenobiotics to which humans are exposed through diet and environment and which possess the same chemical structures (i.e. alicyclic amines such as paroxetine and desloratadine), that would have similar redox properties and cause the same cataracts as postulated for varenicline.

In summary, the rare occurrence of subcapsular cataracts in the clinical trial database, as well as the preclinical findings that varenicline does not distribute to the lens, suggest that this case of subcapsular cataracts is most likely attributable to the patient's smoking history and that varenicline does not contribute to the occurrence of cataracts.

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Acknowledgment: The clinical trial reported in Williams *et al.*⁵ was funded by Pfizer (Clinical Trials Identification Number: NCT00143299). KEW, KRR, CBB, AMP, and JG are all employees of Pfizer.

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Paper [CMRO-4007_4](#), 11:25-25.01.08

Accepted for publication: 28 November 2007

Published Online: 14 January 2008

[doi:10.1185/030079908X261140](https://doi.org/10.1185/030079908X261140)