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CORRESPONDENCE

N-acetylcysteine is unlikely to reduce hospitalisation for chronic obstructive pulmonary disease

To the Editor:

We read with interest the recent paper by GERRITS *et al.* [1] reporting on the effectiveness of *N*-acetylcysteine in reducing re-hospitalisations for chronic obstructive pulmonary disease (COPD). We are concerned, however, that the apparent benefit is actually the result of bias in study design and analysis.

The paper mentions that patients were considered users if they received *N*-acetylcysteine "immediately" after discharge. However, we are not given the definition of "immediately" nor are we provided with the average and range of the length of time from hospital discharge to dispensing of the first prescription for *N*-acetylcysteine. Since follow-up time starts at discharge from hospital for all subjects, irrespective of whether they will or will not be dispensed *N*-acetylcysteine, there is a strong possibility of immortal time bias [2]. Indeed, the time period from discharge to the first dispensing is "immortal" by definition since re-admissions could not occur during this period; if they did occur before the first prescription, the subject would have been classified as "unexposed". Moreover, this immortal time period is in fact unexposed, since the subject has not yet received the drug, but is misclassified as exposed by this approach to data analysis.

Consequently, such misclassified immortal time will cause the rate of re-admission in the "unexposed" to be artificially inflated resulting in an impression of a protective rate ratio for exposure. This bias will also accentuate the apparent dose/response effect, since the daily dose calculation uses the immortal unexposed time and also considers it as exposed. It would be useful to redo these analyses, after properly classifying exposures.

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2. Suissa S. Effectiveness of inhaled corticosteroids in COPD: immortal time bias in observational studies. *Am J Respir Crit Care Med* 2003; 168: 49–53.

From the authors:

We thank S. Suissa and P. Ernst for their interest in our paper [1]. We agree that immortal bias could have invalidated the results of our study if there had been a significant time lag between hospital discharge of patients with chronic obstructive pulmonary disease (COPD) and the start of *N*-acetylcysteine therapy. However, this was not the case. Patients were classified as "exposed" when they showed up with a prescription in the retail pharmacy for *N*-acetylcysteine within a period of 2 days after discharge. When therapy is initiated during hospitalisation, it is common practice in Dutch hospitals that patients receive a few daily dosages of *N*-acetylcysteine to bridge the gap between the time of discharge and the first occasion they can visit their retail pharmacy. In the exposed group with a re-admission for COPD, usage of *N*-acetylcysteine was virtually continuous (87.6% were still using at the time of the second admission). In order to assess the possible impact of exposure variation over time (*e.g.* treatment interruption), we also applied Cox's proportional hazards models with time-dependent exposure classification and found no differences with our initial estimates of the relative risks. For reasons of clarity, we decided to present only the results of the overall use and the average daily dose of *N*-acetylcysteine analyses.

S. Suissa and P. Ernst also point to the possible role of immortal bias in the daily dose calculations, but this comment is inaccurate as only person/time experience was included in the analyses directly derived from the time-windows of measured exposure of *N*-acetylcysteine. The Dutch pharmacy system enforces patients to frequent a single retail pharmacy for their prescription drugs, facilitating the recording of precise start and stop date of therapy.

In assessing the effect of a hypothetical bias, appropriate study designs and analysis are of course pivotal. But the strength of available molecular and clinical evidence of the exposure/outcome association should also be considered. As S. Suissa pointed out, the precise role of inhaled steroids in the treatment of chronic obstructive pulmonary disease is still heavily debated [2]. Although the plea for more cautiousness to prevent immortal bias by S. Suissa and P. Ernst makes absolute sense, it would be a challenge and an imperative next step to show the role of immortal bias in a case of an "established" association, such as the role of inhaled steroids in the prevention of asthma rehospitalisations [3]. Variations in time-windows used for denominator data always have an impact on risk estimates, as shown by SUISSA [2] in analyses with exposures of inhaled β-agonists in relation to chronic obstructive pulmonary disease morbidity and mortality and also shown for other drug exposures [4].

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