Benzodiazepine drug use and adverse respiratory outcomes among older adults with COPD

To the Editor:

We read with interest the recent article by Vozoris *et al.* [1], who suggest that benzodiazepine drug use had adverse respiratory outcomes among older adults with chronic obstructive lung disease (COPD). Many studies are in support of this study but we cannot neglect the opposing studies which did not show any adverse effects of benzodiazepines in patients with COPD [2, 3]. American Thoracic Society/European Respiratory Society guidelines [4] state that hypnotics should not be given in patients with "severe" COPD. It would be better if the authors could stage COPD according to the Global Initiative for Chronic Obstructive Lung Disease guidelines. Studies of lower dose benzodiazepines and lower dose opioids in patients with COPD were not associated with increased admissions [5].

The prevalence of insomnia in COPD patients is ~50% [6], which has a negative impact on the quality of life of these patients. Therefore, the quality of life of COPD patients can be improved by improving sleep quality and anxiety. Although there is no relationship of problems associated with sleep with lung function [6–8], there may be a relationship between the frequency and severity of pulmonary symptoms [6].

Benzodiazepines differ from each other by their duration of action and pharmacokinetics, and can be divided into short-, intermediate- or long-acting agents. One study showed that a long-acting benzodiazepine had more adverse effects on the respiratory system than a short-acting benzodiazepine [9].

We agree with the authors that strict vigilance on adverse effects of benzodiazepines in older COPD patients is required, as this group of patients have altered pharmacokinetics due to the presence of comorbid conditions, as well as medications for these conditions that may affect metabolism of benzodiazepines. In addition, short-acting benzodiazepines in adequate doses can improve quality of life in elderly patients.

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Short-acting benzodiazepines can be safely used in COPD and might improve quality of life in the elderly http://ow.ly/DgvXw

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From the authors:

We thank R. Katyal for his comments on our study as he raises some interesting points. Although there are some other physiology studies showing no association between benzodiazepine receipt and negative respiratory effects among individuals with chronic obstructive pulmonary disease (COPD) [1, 2], physiology studies are limited in their ability to provide information on the true clinical impact of benzodiazepines in the COPD population. This is because they generally include small numbers of participants, administration of only a single benzodiazepine dose, short follow-up and do not examine for clinically meaningful respiratory outcomes. In contrast, our study [3] included a large population-based sample, real-world benzodiazepine doses and durations, a longer follow-up period, and important and relevant clinical respiratory outcomes.

R. Katyal writes that it would have been helpful to see an analysis of benzodiazepine-related adverse respiratory effects by COPD severity "according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines", probably referring to the forced expiratory volume in 1 s (FEV_1) staging system. The health administrative data on which our analysis was based did not contain patient-level clinical information, such as lung function measurements. Newer GOLD guidelines have moved away from classifying COPD severity by FEV_1 level alone, and instead use a combined assessment that incorporates COPD exacerbation history [4]. We explain in our supplementary material that COPD exacerbation history is an important marker of disease severity [3], being associated both with severity of underlying airflow obstruction [5] and mortality [6], and that it is also the single best predictor of future COPD exacerbation, regardless of lung function [7]. We performed a sensitivity analysis reporting outcomes stratifying by COPD exacerbation history in the year prior to index and consistently showed an increased risk of several negative respiratory outcomes among benzodiazepine users across subgroups of differing COPD exacerbation history. This analysis supports the claim that benzodiazepine use is associated with adverse respiratory outcomes regardless of COPD severity.

R. Katyal states that receipt of lower doses of benzodiazepines among individuals with COPD are not associated with increased hospital admission risk and cite a study by Klink *et al.* [8] to support this statement. However, the study by Klink *et al.* [8] does not report data on benzodiazepine drug receipt or hospital admissions. A paper by Ekström *et al.* [9] shows no increased risk of all-cause hospitalisation among prevalent benzodiazepine users with oxygen-dependent COPD, regardless of drug dose. However, in the study by Ekstrom *et al.* [9], respiratory-specific hospitalisations were not examined and prevalent (and not incident) benzodiazepine receipt was considered. In addition, the authors' approach to quantify drug dose is questionable, as individuals are often given flexibility by their doctors regarding the frequency with which they use benzodiazepines, making accurate benzodiazepine dose quantification challenging.

As mentioned by R. Katyal, sleep symptoms are present with increased frequency among individuals with COPD with more respiratory symptoms [8], thereby implying that our finding of increased adverse respiratory outcomes among older adult benzodiazepine users with COPD may be confounded by the presence of sleep symptomatology. However, our propensity-score matched analysis included doctor-diagnosed sleep disorders and new and non-benzodiazepine users were well-matched on this health characteristic, making confounding as a result of this factor unlikely (table 1 in [3]).

We agree that benzodiazepine half-life may impact risk of negative respiratory outcomes and R. Katyal references a physiology study showing worse adverse respiratory effects following administration of a longer-acting benzodiazepine (flunitrazepam) *versus* a short-acting agent (triazolam) [2]. In our supplementary material [3], we analysed adverse respiratory outcomes stratifying by the half-life of the benzodiazepine received. We reported that both long-acting and intermediate/short-acting benzodiazepines were significantly associated with important adverse respiratory outcomes, with slightly higher relative risks among users in the intermediate/short-acting subgroup compared to the long-acting subgroup. Others have similarly reported that benzodiazepine-related psychomotor effects are not related to medication half-life [10].