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Letter to the Editor

Opioids in COPD: the 'whole picture' includes results from real-world, population-based observational studies

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We thank Currow *et al*. for their interest in our work [1] and for their comments. We respectfully point out that we did not condemn in our paper the careful prescription of low dose opioids for refractory dyspnoea in selected patients with advanced COPD. We have also not used exaggerated language in our paper, such as 'disasters await clinicians who prescribe opioids in people with COPD', as Currow *et al*. have written. On the contrary, we have acknowledged in our introduction the results of several clinical trials showing that systemic opioids can safely reduce dyspnoea in individuals with advanced COPD and that several respiratory guidelines support the use of opioids in COPD for refractory dyspnoea [1].

The purpose of our paper was explicitly stated: 'to describe the scope, pattern, and patient characteristics associated with incident opioid use among older adults with COPD' [1]. While selected COPD patients may indeed benefit from carefully prescribed opioids for refractory dyspnoea, the results of our 'real-world', population-based study show that opioids are not being used in such a manner among older adults with COPD. Our study results show that frequent drug use, patterns potentially indicative of excessive usage, drug receipt during periods of acute respiratory exacerbation and drug receipt among individuals with concerning comorbidities characterize incident opioid use in the older adult COPD population in Ontario, Canada [1]. We feel that these drug use patterns in opioid-naive individuals do raise *potential* safety concerns. Previously published observational research by Currow *et al*. using Swedish health administrative data also support the observation that carefully prescribed, low dose opioids are not the norm in vulnerable patients with advanced COPD. The majority of opioid recipients (298/509 or 59%) were receiving what the authors defined as high dose opioids (>30 mg oral morphine equivalents day^{-1}) and this was found to be associated with increased all-cause mortality risk [2].

There is nothing sinister about the fact that we did not present data relating to possible adverse respiratory outcomes associated with incident opioid drug use in our paper. We were explicit about the purpose of the present study and our future plans: 'our present focus was on describing patterns of opioid use in the older adult COPD population. Examining for potential respiratory-related health outcomes of opioid use among older adults with COPD will be undertaken next' [1]. We kindly ask that Currow *et al*. stay tuned for our future work.

While several clinical trials demonstrate that opioids can reduce refractory dyspnoea in advanced COPD, it is also important to consider the features of these trials that limit their ability to evaluate adequately and comprehensively for possible drug harms: small numbers of subjects, selected subjects (e.g. individuals with certain comorbidities or individuals with a history of previous adverse reactions to opioids were sometimes excluded), low or single opioid dosing levels, short follow-up durations and subjects who perceived no benefit, experienced adverse events or died, were sometimes excluded from final analyses. In contrast, population-based observational studies are well-suited to evaluate for possible drug-related adverse events, as they typically include larger numbers of subjects, individuals that clinical trials often exclude (e.g. those with comorbidities), longer follow-up durations, 'real-world' drug dosing and use and less subject drop-out. While we agree that confounding by indication cannot be entirely eliminated in observational studies evaluating drug harm, this bias can be minimized by employing certain methods, such as evaluating for adverse outcomes

among individuals with differing disease severity, including those with the least severe disease, in whom confounding by indication is less likely to be an issue [3]. Results of 'real-world', population-based, observational studies complement the results of clinical trials and help give a more complete picture regarding the use, and potential benefits and adverse effects, of drug therapy [4].

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare NTV had support from The Lung Association-Canadian Thoracic Society National Grant Review/Grant-In-Aid for the submitted work, SSG and DO had no support from any organization for the submitted work, DO received grants and personal fees from Boehringer Ingelheim, grants and personal fees from Astra Zeneca, grants from GlaxoSmithKline, personal fees from Novartis, in the previous 3 years and NTV and SSG had no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years. NTV, SSG and DO had no other relationships or activities that could appear to have influenced the submitted work.

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