Correspondence: James Downar, Dept of Medicine, University of Toronto, 200 Elizabeth St. 9N-926, Toronto, ON, Canada. E-mail: james.downar@utoronto.ca

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References

1 Vozoris NT, Wang X, Fischer HD, *et al.* Incident opioid drug use and adverse respiratory outcomes among older adults with COPD. *Eur Respir J* 2016; 48: 683–693.
2 Ray WA, Chung CP, Murray KT, *et al.* Prescription of long-acting opioids and mortality in patients with chronic noncancer pain. *JAMA* 2016; 315: 2415–2423.
3 Neutel CI, Johansen HL. Association between hypnotics use and increased mortality: causation or confounding? *Eur J Clin Pharmacol* 2015; 71: 637–642.
4 Ekstrom MP, Bornefalk-Hermansson A, Abernethy AP, *et al.* Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. *BMJ* 2014; 348: g445.
5 Freemantle N, Marston L, Walters K, *et al.* Making inferences on treatment effects from real world data: propensity scores, confounding by indication, and other perils for the unwary in observational research. *BMJ* 2013; 347: f6409.
6 Currow DC, McDonald C, Oaten S, *et al.* Once-daily opioids for chronic dyspnea: a dose increment and pharmacovigilance study. *J Pain Symp Manage* 2011; 42: 388–399.
7 Rocker GM, Simpson AC, Young J, *et al.* Opioid therapy for refractory dyspnea in patients with advanced chronic obstructive pulmonary disease: patients' experiences and outcomes. *CMAJ Open* 2013; 1: E27–E36.
8 Abernethy AP, Currow DC, Frith P, *et al.* Randomised, double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea. *BMJ* 2003; 327: 523–528.
9 Marciniuk DD, Goodridge D, Hernandez P, *et al.* Managing dyspnea in patients with advanced chronic obstructive pulmonary disease: a Canadian Thoracic Society clinical practice guideline. *Can Respir J* 2011; 18: 69–78.

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From the authors:

We thank J. Downar and colleagues for their interest in our study [1] and their contributions to this important clinical issue. Downar and colleagues view our findings through the lens of palliative medicine. We recognise the role of opioids for symptom relief among individuals with chronic obstructive pulmonary disease (COPD) as part of end-of-life care. We intentionally excluded individuals who were receiving palliative care from our study, acknowledging that "goals of care and indications for opioid use may differ in this context" [1]. Our goal was instead to evaluate, from a respiratory safety perspective, the use of opioid drugs among the broader older adult COPD population. Our previous work on opioids in COPD [2] suggests that musculoskeletal pain is probably the main reason for opioid drug receipt in the older adult COPD population rather than respiratory symptoms. Opioids combined with non-opioid agents, like acetaminophen or aspirin, accounted for close to 90% of opioid use among older adults with COPD [2]. These combination opioid/non-opioid agents are unlikely to be used in end-of-life care and their use more likely reflects treatment of musculoskeletal pain, which commonly occurs in COPD [3, 4]. Opioids were also less commonly used among individuals with COPD with frequent exacerbations [2] and this group is more likely to be troubled by refractory respiratory symptoms. Less common use of opioids by these individuals supports the argument that opioids are prescribed for reasons other than palliation of respiratory symptoms.

Downar and colleagues suggest that our study findings may have been influenced by possible residual confounding by indication. While we acknowledged this possibility, we undertook several steps to minimise confounding. First, we excluded individuals receiving palliative care, since this group is near the end-of-life as a result of disease and opioids may be appropriately indicated in that setting. Second, our analyses were adjusted for a total of 33 different covariates, many of which are indicators of COPD severity, including respiratory exacerbation history, duration of COPD, receipt of respiratory medications and presence of various comorbidities. We think it is unlikely that our results would be rendered nonsignificant if we additionally adjusted for one more covariate, dyspnoea symptoms, if this information were available to us. Third, we performed a sensitivity analysis examining for adverse respiratory outcomes associated with opioid use, distinguishing by COPD exacerbation history. COPD exacerbation history is the single best predictor of future exacerbation [5] and it is also associated with mortality [6]. We found increased all-cause mortality among incident opioid users, even in the healthiest subgroup with no exacerbations in the year prior to index [1]. Finally, we re-ran our analyses excluding individuals with lung malignancy and any malignancy, as these conditions might reflect palliative indications for opioid use. Significantly increased respiratory-related morbidity and mortality persisted even after excluding individuals with lung malignancy and any malignancy [1]. We feel that these steps help support our interpretation of the study findings.

We offered explanations in our article [1] regarding why hazard ratios for some adverse respiratory outcomes may have been higher in the lower-dose *versus* the higher-dose opioid category. With certain types of drugs, such as opioids, patients can be given discretion from their prescribers regarding drug frequency and dose used, thereby potentially resulting in some degree of misclassification in the daily dose exposure estimates. Furthermore, for practical reasons, when determining the daily opioid dose for individuals receiving long-acting opioids, we did not consider possible concomitant receipt of shorter-acting opioid agents. While Downar and colleagues are correct that, when considering all opioid use among community-dwelling individuals, the number needed to harm (NNH) for all-cause mortality is 125, when one considers opioid-only agents, the NNH for all-cause mortality was considerably lower at 28 (based on an absolute risk difference of 3.6%, see table 4 in [1]). The NNH for all-cause mortality was even lower at 11 for long-term care residents who were opioid users (based on an absolute risk difference of 9.3%, see supplement 2 in [1]).

We respectfully disagree with Downar and colleagues that clinical trials are best for evaluating possible drug harms. Clinical trials of opioids in COPD to date are limited in their ability to adequately evaluate for possible drug harm given the following: small numbers of subjects; exclusion of individuals with comorbidities or previous adverse reaction to opioids; evaluation of low or single opioid doses; and significant subject drop-out. There have been concerns raised about the reporting of harm data in clinical trials in other conditions experienced by older adults [7]. In contrast, population-based observational studies, such as ours [1], are well-suited to evaluate for possible drug harms, as they typically include more individuals, particularly ones that clinical trials often exclude, as well as "real-world" drug dosing and patterns of use. Observational drug studies should be embraced as complementary to clinical trials, to help give a more complete picture of therapy benefits and harms [8].

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New opioid drug use is associated with increased respiratory-related morbidity and mortality in nonpalliative COPD http://ow.ly/wRfb303k4Yl

Nicholas T. Vozoris[1,2,3], Denis E. O'Donnell[4], Chaim M. Bell[3,5,6,7], Sudeep S. Gill[4,5] and Paula A. Rochon[3,5,6,8]
[1]Division of Respirology, Dept of Medicine, St. Michael's Hospital, Toronto, ON, Canada. [2]Keenan Research Centre in the Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, ON, Canada. [3]Dept of Medicine, University of Toronto, Toronto, ON, Canada. [4]Dept of Medicine, Queen's University, Kingston, ON, Canada. [5]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada. [6]Institute of Health Policy, Management, and Evaluation, University of Toronto, Toronto, ON, Canada. [7]Division of General Internal Medicine, Dept of Medicine, Mount Sinai Hospital, Toronto, ON, Canada. [8]Women's College Research Institute, Women's College Hospital, Toronto, ON, Canada.

Correspondence: Nicholas T. Vozoris, Division of Respirology, Dept of Medicine, St. Michael's Hospital, 30 Bond Street, Toronto, ON, Canada, M5B 1W8. E-mail: nick.vozoris@utoronto.ca

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References

1 Vozoris NT, Wang X, Fischer HD, *et al.* Incident opioid drug use and adverse respiratory outcomes among older adults with COPD. *Eur Respir J* 2016; 48: 683–693.
2 Vozoris NT, Wang X, Fischer HD, *et al.* Incident opioid drug use among older adults with chronic obstructive pulmonary disease: a population-based cohort study. *Br J Clin Pharmacol* 2016; 81: 161–170.
3 Borge CR, Wahl AK, Moum T. Pain and quality of life with chronic obstructive pulmonary disease. *Heart Lung* 2011; 40: e90–e101.
4 Elkington H, White P, Addington-Hall J, *et al.* The healthcare needs of chronic obstructive pulmonary disease patients in the last year of life. *Palliat Med* 2005; 19: 485–491.
5 Hurst JR, Vestbo J, Anzueto A, *et al.* Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010; 363: 1128–1138.
6 Connors AF Jr, Dawson NV, Thomas C, *et al.* Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). *Am J Respir Crit Care Med* 1996; 154: 959–967.
7 Lee PE, Fischer HD, Rochon PA, *et al.* Published randomized controlled trials of drug therapy for dementia often lack complete data on harm. *J Clin Epidemiol* 2008; 61: 1152–1160.
8 Vandenbroucke JP, Psaty BM. Benefits and risks of drug treatments: how to combine the best evidence on benefits with the best data about adverse effects. *JAMA* 2008; 300: 2417–2419.