

## Letter to the Editor

# Opioids in chronic obstructive pulmonary disease: the whole picture using all available evidence

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Vozoris *et al.* are to be commended for their continued work on population patterns of prescribing in people with chronic obstructive pulmonary disease (COPD) [1, 2].

The burden of pain and breathlessness in people with COPD is clearly quantified [3]. More than 90% of people with advanced COPD have breathlessness at rest or on minimal exertion and between one third and two thirds have pain [3]. Symptom control is necessary in order to avoid a range of morbidities. Having long term, uncontrolled pain or breathlessness is a cause of significant suffering, and is intolerable when, for example, evidence supports the effective and safe use of regular low dose sustained release morphine for chronic refractory breathlessness [4, 5].

Vozoris *et al.* imply in this paper that disasters await clinicians who prescribe opioids in people with COPD for symptom relief [1]. The paper refers to 'significant risks' when the data presented and references cited are non-randomized studies that describe observed 'associations' only. Neither paper [1, 2] can demonstrate a causal relationship between prescribing and any subsequent outcomes. Neither study controls for potential confounders and, even were this to be done, causality still cannot be assigned [6].

The data presented by Vozoris *et al.* do not support the authors' conclusion that 'potential safety concerns are raised by the degree and pattern of new opioid use' in people with COPD [1]. Of particular interest in the current paper is what is *not* reported. Using an identical methodology and a similar cohort, the same authors reported the associations between recent prescriptions of benzodiazepines and increased exacerbations of COPD and increased presentations to the Emergency Department (ED) [2]. However, the current paper is silent about any associations with worsening of COPD or ED presentations [1].

Sicker people have a greater symptom burden, are prescribed more medications for symptom control, have more frequent exacerbations and more frequent presentations to the ED. If clinicians are reluctant to use a treatment, then often its use is delayed until there is a crisis. Such under-treatment might result in an even stronger, but still spurious, association between the treatment and any adverse outcome.

Data from adequately powered randomized controlled trials are required to inform the net effects of opioids in the setting of people with COPD such as benefits and harms collected using standardized assessments [7]. Such studies need to be complemented with detailed prospective pharmacovigilance studies in real world clinical settings quantifying adverse events and benefits [8].

Ultimately, the judicious use of opioids in people with COPD is justified and to preclude their use would continue to condemn a large population internationally to poor symptom control [9]. Work needs to continue urgently to define the population who will most benefit from opioids safely in COPD [10] and ensure that it becomes a registered indication for the treatment of chronic refractory breathlessness (at rest or on minimal exertion) so that clinicians can reduce avoidable suffering. The myths that have arisen around the use of regular low dose morphine in severe COPD need to be dispelled urgently.

## Competing Interests

All authors have completed the Unified Competing Interest form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) (available on request from the corresponding author) and declare no

support from any organization for the submitted work, DC was a consultant to Mayne Pharma in the previous last 3 years and there are no other relationships or activities that could appear to have influenced the submitted work.

## REFERENCES

- 1 Vozoris NT, Wang X, Fischer HD, Gershon AS, Bell CM, Gill SS, O'Donnell DE, Austin PC, Stephenson AL, Rochon PA. Incident opioid drug use among older adults with chronic obstructive pulmonary disease: a population-based cohort study. *Br J Clin Pharmacol* 2016; 81: 161–70.
- 2 Vozoris NT, Fischer HD, Wang X, Stephenson AL, Gershon AS, Gruneir A, Austin PC, Anderson GM, Bell CM, Gill SS, Rochon PA. Benzodiazepine drug use and adverse respiratory outcomes among older adults with COPD. *Eur Respir J* 2014; 44: 332–40.
- 3 Solano JP, Gomes B, Higginson IJ. A comparison of symptom prevalence in far advanced cancer, AIDS, heart disease, chronic obstructive pulmonary disease and renal disease. *J Pain Symptom Manage* 2006; 31: 58–69.
- 4 Ekström M, Nilsson F, Abernathy AP, Currow DC. Effects of opioids on breathlessness and exercise capacity in chronic obstructive pulmonary disease. A systematic review. *Ann Am Thoracic Soc* 2015; Jul. 12: 1079–92.
- 5 Ekström MP, Bornefalk-Hermansson A, Abernathy AP, Currow DC. Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. *Br Med J* 2014; 348: g445.
- 6 Bosco JL, Silliman RA, Thwin SS, Geiger AM, Buist DS, Prout MN, Yood MU, Haque R, Wei F, Lash TL. A most stubborn bias: no adjustment method fully resolves confounding by indication in observational studies. *J Clin Epidemiol* 2010; 63: 64–74.
- 7 Australian and New Zealand Clinical Trials Registry (ANZCTR). Available at <http://www.anzctr.org.au/> (accessed 22 Nov 2015) ACTRN12609000806268.
- 8 Currow DC, Rowett D, Doogue M, To THM, Abernathy AP. An international initiative to create a collaborative for pharmacovigilance in hospice and palliative care clinical practice. *J Palliat Med* 2012; 15: 282–6.
- 9 Ekstrom M, Abernathy AP, Currow DC. The management of chronic breathlessness in patients with advanced and terminal illness. *Br Med J* 2015; 349: g7617.
- 10 Johnson MJ, Bland JM, Oxberry SG, Abernathy AP, Currow DC. Opioids for chronic refractory breathlessness: patient predictors of beneficial response. *Eur Respir J* 2013; 42: 758–66.

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