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Low-dose opioids should be considered for symptom relief also in advanced chronic obstructive pulmonary disease (COPD)

Magnus Ekström,^{1,2} Anna Bornefalk-Hermansson,³
Amy Abernethy,⁴ David Currow²

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¹Division of Respiratory Medicine & Allergology, Department of Clinical Sciences, Lund University, Lund, Sweden

²Discipline, Palliative and Supportive Services, Flinders University, Adelaide, South Australia, Australia

³Uppsala Clinical Research Center, Uppsala University Hospital, Uppsala, Sweden

⁴Division of Medical Oncology, Department of Medicine, Duke University Medical Center, Durham, North Carolina, USA

Correspondence to
Dr Magnus Ekström,
Department of Medicine,
Blekinge Hospital, Karlskrona
SE-37185, Sweden;
pmekstrom@gmail.com.



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We read with interest the comments by Dr Vozoris¹ on our paper “Safety of benzodiazepines and opioids in very severe respiratory disease.”² We are concerned that his comments might give the impression that opioids should *not* be used in patients with severe chronic obstructive pulmonary disease (COPD). This could contribute to symptomatic undertreatment and unnecessary suffering.

The main finding of the study should be emphasised: treatment with regular, low-dose opioids (≤ 30 mg oral morphine equivalents per day) was not associated with increased rates of hospitalisation or death in people with severe, oxygen-dependent COPD.

The focus of Vozoris’¹ comments was that patients treated with benzodiazepines or high-dose opioids had increased adjusted mortality compared with patients who were not on these treatments. This is an association, *not* a cause–effect relationship. Such an association is not surprising, as increased mortality could reflect that the medications (and higher doses) are more likely to be used in patients with more severe symptoms as their illness worsens, especially in the last weeks or days of life. Such associations (confounding by indication or underlying disease severity) often persist in non-randomised trials despite adjustment strategies, as adjusting can account only for measured confounders.³ However, this makes the main finding of a lack of association between low-dose opioids and mortality or hospitalisations even more notable in this vulnerable, oxygen-dependent population.²

The findings in this current study that regular low-dose opioids are safe in people with oxygen-dependent COPD are consistent with available phase III and phase IV trials. This includes a pharmacovigilance study of 85 patients with advanced disease (54% with COPD) treated with up to 30 mg opioids daily during more than 30 patient-years of follow-up.⁴ Efficacy of opioids for relief of breathlessness was shown in an

adequately powered randomised trial.⁵ Our low-dose category was chosen from that study.^{4 5}

Further work is needed to understand the reasons for, and outcomes from higher doses of benzodiazepines and/or opioids, which were used by 21% (not $\geq 50\%$ as stated by Vozoris¹) of study patients. We agree with Vozoris on the need to “monitor for side-effects when prescribing these drugs to vulnerable advanced patients with COPD.”

Given the evidence to date of efficacy and safety, regular, low-dose, sustained release morphine should be considered for the relief of breathlessness in patients with severe COPD.

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