

# The need for greater opioid pharmacovigilance in COPD

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## Dear editor

I read with interest the article by Ahmadi et al<sup>1</sup> that described the use of prescription opioid drugs among Swedes with advanced COPD. The authors are to be commended for their research work on this important clinical topic. I would like to bring to the attention of your readers several points though.

First, the authors presented the following striking data: ~50% of individuals with advanced COPD were dispensed opioids and 97% of these dispensings were intended to treat pain.<sup>1</sup> However, several recent Cochrane reviews have concluded that there is insufficient evidence to support the use of opioids for treating chronic musculoskeletal pain.<sup>2-5</sup> I was surprised to see that the authors did not explicitly comment in the discussion on the finding that opioids were frequently used by individuals with advanced COPD for a reason for which there is a lack of supportive evidence.

Second, the authors stated that the very low number of opioid dispensings for dyspnea supports that breathlessness is undertreated in advanced COPD. There may indeed be some truth to this. However, among individuals with COPD dispensed opioids in this study, the vast majority surprisingly had only World Health Organization class 1 (37%) or class 2 (33%) performance status<sup>1</sup> (with class 1 performance status defined as “restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work and office work”<sup>6</sup>). Therefore, another possible explanation for the finding of a very low number of opioid dispensings for dyspnea in this study is that many individuals with advanced COPD in this cohort may have had respiratory symptoms reasonably lessened with more traditional COPD management and the addition of opioids was simply not required.

Third, the authors wrote that “the evidence to date supports the safety of low-dose opioids for symptomatic treatment in advanced diseases including COPD”.<sup>1</sup> However, many of the studies they referenced to support this statement were clinical trials specifically designed to evaluate opioid efficacy and not possible harm. Clinical trials of treatment efficacy are often limited in their ability to comprehensively evaluate for possible drug harms given that they are usually characterized by small participant numbers, exclusion of individuals at risk for drug-related adverse events (such as those with comorbid illnesses and those with a history of previous drug-related adverse events), limited drug dosing examination, and significant participant drop out. Furthermore, the authors did not reference the results of a recent, large, population-based, observational study, designed to evaluate for possible drug-related adverse events that found increased respiratory-related morbidity and mortality among older adults with COPD receiving incident opioids, including those receiving low-dose formulations.<sup>7</sup>

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Fourth, the authors did not present data on opioid drug dose in their study, although they acknowledged in the “Methods” section having this information available in their data set.<sup>1</sup> In a previous study by this same group of researchers using the same data set, the authors reported that the majority (298/509 or 58.5%) of individuals with COPD receiving opioids were receiving what the authors termed “high dose”.<sup>8</sup> Furthermore, in that same study, the researchers found that the use of “high-dose” opioids among individuals with COPD was associated with significantly increased risk of all-cause mortality.<sup>8</sup> These results raise serious concerns regarding opioid use and outcomes among individuals with COPD.

In conclusion, although there is evidence to support the careful use of opioids for refractory respiratory symptoms among selected individuals with COPD, Ahmadi et al<sup>1</sup> show that opioid drugs (whose use has been found to be associated with adverse outcomes<sup>7,8</sup>) are all too frequently given to individuals with advanced COPD and for a reason that is not currently supported by scientific evidence (ie, chronic musculoskeletal pain).<sup>2-5</sup> Health care professionals need to advocate and practice greater opioid pharmacovigilance in COPD.

## Disclosure

The author reports no conflicts of interest in this communication.

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## Authors' reply

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## Dear editor

We thank Dr Vozoris for his insightful comments on our paper.<sup>1</sup>

The use of opioids for treating pain and the underlying evidence base for this indication was not the scope of our article. Although we agree that the evidence for treatment with opioids for “chronic” musculoskeletal pain is inconsistent or weak, we had insufficient data to determine symptom severity and whether the patients were prescribed opioids for chronic or acute pain. It should also be considered that the cited Cochrane reviews on opioids for chronic pain have weak evidence for their conclusions.<sup>2,3</sup> The review of long-term effectiveness and safety of opioid therapy for chronic noncancer pain by Noble et al<sup>2</sup> included 25 case series and only 1 randomized controlled trial. The clinician should carefully weigh the risk versus benefit of opioids in pain treatment, especially in the setting of clinical instability and in chronic pain. However, we think that there are many situations where opioids have an important role in treating severe distressing pain, where failure to use opioids might contribute to unnecessary suffering and treatment nihilism.

The majority of patients had World Health Organization (WHO) functional class 1 or 2 in our study and Dr Vozoris suggests that their respiratory symptoms may have been relieved by more traditional COPD management and that symptomatic treatment with opioids was simply not required. There are strong data to disagree with this statement. These patients had end-stage COPD with chronic respiratory failure with a median survival time of 1.9 years.<sup>4</sup> Breathlessness is very common in patients with very severe COPD<sup>5</sup> and a high proportion of patients suffer from chronic breathlessness, despite intensive COPD treatment.<sup>6</sup> In a recent study of less severely ill COPD patients, chronic breathlessness

that significantly compromised function was present in 74% of patients, despite combined inhaled triple therapy and physiotherapy.<sup>6</sup> Given the evidence base for the efficacy of low-dose opioids for safely reducing chronic breathlessness, our finding that only 2% of opioid prescriptions were for breathlessness strongly supports the assertion that there is systematic undertreatment of people with chronic breathlessness and advanced COPD.

Data on the dispensed opioid doses are presented in Table 2 as WHO defined daily doses per prescription.<sup>1</sup> More details regarding dispensed doses at the time of starting long-term oxygen therapy have been published separately.<sup>7</sup> The average dispensed prescription in this study was for short-term treatment of a mean of 9.3 (interquartile range, 3.7–16.7) defined daily doses of morphine equivalents in milligrams of morphine per prescription.

Low-dose sustained release oral morphine is the pharmacological treatment with the best evidence base for relieving chronic breathlessness in advanced COPD, and the risk of serious adverse events (respiratory depression, hospitalization, or death) does not seem to increase by low-dose morphine in the short term.<sup>8</sup> The observational, registry-based study by Vozoris et al reported increased respiratory-related morbidity and mortality among COPD patients receiving incident opioids. The 30-day mortality risk was 1.9% versus 1.1% in people without an opioid prescription after propensity score matching; an absolute difference of 0.8% in a population where the prescription likely was for symptom control in relation to clinical deterioration and late in life where increased risk of death was the expected outcome.<sup>9</sup> Furthermore, stronger opioids were associated with “lower” risk than weaker opioids and information was lacking on prevalence and severity of symptoms, degree of clinical safety, and why, how, or at what dose the opioid was used.<sup>9</sup> In a previous analysis in patients with oxygen-dependent COPD, treatment with opioids in low doses ( $\leq 30$  mg opioid equivalents per day) was not associated with increased risk of hospitalization or death.<sup>7</sup>

We commend Vozoris et al for taking forward high-quality safety studies in this important area. Combined efforts are needed to further determine the suitable target population and clinical net benefit of low-dose opioids for symptomatic control in patients with severe illness.

## Disclosure

The authors report no conflicts of interest in this communication.

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