Prescription opioid use in advanced COPD: benefits, perils and controversies

To the Editor:

In the ancient Roman literary masterpiece *Metamorphoses*, the poet Ovid writes that the god of sleep, Somnus (who had a twin brother named Thanatos, or Death), lived in a dark cave and "in front of the cave mouth a wealth of poppies flourish" [1]. This verse demonstrates that our ancestors recognised links between sleep, death and the poppy plant (from which opium is derived). Present-day population-based studies show that opioid drugs are used frequently [2, 3] and in other potentially concerning ways [2] among individuals with chronic obstructive pulmonary disease (COPD), including those with nonpalliative disease [2]. Several guidelines [4–6] support using opioids for refractory respiratory symptoms in advanced COPD, which is a commonly encountered and challenging problem. The report by Politis *et al.* [7] in the *European Respiratory Journal* describes a case of respiratory depression in an individual with advanced COPD following receipt of prescription opioids for dyspnoea, providing a timely reminder of the serious negative respiratory effects opioids can potentially have in vulnerable COPD patients.

Several interesting points for discussion emerge from the case report. First, the timing of opioid drug receipt and the adverse event in the case is noteworthy. Although this patient with advanced COPD suffered from chronic, severe exertional dyspnoea (without frequent respiratory exacerbations), and although this is the precise clinical setting in which opioids have been evaluated and found to be efficacious [8–11], he did not receive opioids pre-hospitalisation. Instead, he first received opioids while hospitalised with a presumed acute infectious COPD exacerbation, which is a setting in which opioid therapy has not been evaluated [8–11] and at least one guideline makes explicit that opioids should be used "in stable patients" with advanced COPD [6]. However, he tolerated opioid therapy well and benefitted from it while in hospital for an acute infectious exacerbation, and opioid-related respiratory depression instead occurred 9 days following hospital discharge, when he was presumably in a more respiratory-stable state. The timing of the patient's opioid receipt and adverse event challenges current perceptions of when opioids can potentially be used in advanced COPD (*i.e.* only in the setting of stable chronic dyspnoea) and when adverse respiratory events can potentially occur (*i.e.* only if given during periods of respiratory status instability).

Second, the opioid regimen used in the case is interesting. It consisted of standing, twice-daily, long-acting, oral tablet morphine plus immediate-release, liquid morphine as required every 4–6 h for breakthrough. While this regimen consisting of both standing and *pro re nata* opioids may be commonly used in chronic pain or palliative care settings, its efficacy and safety have not been specifically examined for refractory dyspnoea management in COPD. Instead, two approaches to prescribing opioids for advanced dyspnoea in COPD are presently outlined in the literature (one formulated by a group of Australian physicians [10–11] and the other by Canadian physicians [6, 9]) and neither approach was used in this specific case. The "Australian approach" consists of once-daily, sustained-release, oral tablet morphine sulfate (10–30 mg) [10–11]. The "Canadian approach" consists of standing, immediate-release, liquid morphine sulfate (starting at 0.5 mg twice daily) with possible weekly up-titration based on clinical re-evaluation, followed by possible eventual substitution with a sustained-release preparation [6, 9]. While the latter Canadian approach is characterised by a more cautious introduction of opioids in the setting of advanced COPD, incorporating prudent elements of prompt and repeated patient re-evaluation, it is noteworthy that it involves, at least initially, giving immediate-release, liquid morphine, inadvertent misuse of which got the patient in this specific case into trouble [7]. Compared to tablet-formulation opioids, liquid morphine may be more challenging for patients to self-administer, as it requires cognitive skill to correctly calculate the amount of liquid to draw based on the liquid's concentration, as well as technical ability to correctly draw the prescribed amount of liquid.

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Patient and drug regimen selection important with opioid use in advanced COPD, given adverse respiratory event risk http://ow.ly/LNXJ30bPD6C

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Third, it is notable that the patient in this case unintentionally misused the immediate-release, liquid morphine prescribed despite receiving "verbal and written education…by a pharmacist prior to discharge" [7]. Even following his adverse respiratory event and further education efforts, he was still unable to safely self-administer immediate-release, liquid morphine. This highlights that in least in some patients, adequate drug counselling cannot overcome the risk of adverse events associated with unsupervised opioid drug self-administration at home. The fact that individuals with COPD tend to be older in age and have multiple comorbidities makes this group particularly vulnerable to potential opioid-related dosing error and toxicity.

While opioids can be effective at reducing troublesome refractory respiratory symptoms in individuals with advanced COPD, the report by Politis *et al.* [7] reminds us that adverse respiratory events associated with opioid drug use are real and potentially serious. While more research on this therapeutic approach is needed, in the interim, careful thought must be given to both patient and drug regimen selection if initiating opioids.

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References

1 Ovid. The Metamorphoses. Seattle, Poetry in Translation, 2000.
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 Ahmadi Z, Bernelid E, Currow DC, *et al.* Prescription of opioids for breathlessness in end-stage COPD: a national population-based study. *Int J Chron Obstruct Pulmon Dis* 2016; 11: 2651–2657.
4 Lanken PN, Terry PB, Delisser HM, *et al.* An official American Thoracic Society clinical policy statement: palliative care for patients with respiratory diseases and critical illnesses. *Am J Respir Crit Care Med* 2008; 177: 912–927.
5 Mahler DA, Selecky PA, Harrod CG, *et al.* American College of Chest Physicians consensus statement on the management of dyspnea in patients with advanced lung or heart disease. *Chest* 2010; 37: 674–691.
6 Marciniuk D, 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.
7 Politis J, Le B, Smallwood N. Respiratory depression secondary to morphine use in a patient with chronic obstructive pulmonary disease and refractory breathlessness. *Eur Respir J* 2017; 49: 1601858.
8 Jennings AL, Davies AN, Higgins JP, *et al.* A systematic review of the use of opioids in the management of dyspnoea. *Thorax* 2002; 57: 939–944.
9 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.
10 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.
11 Currow DC, McDonald C, Oaten S, *et al.* Once-daily opioids for chronic dyspnea: a dose increment and pharmacovigilance study. *J Pain Symptom Manage* 2011; 42: 388–399.

From the authors:

We thank N.T. Vozoris for his comments and interest in the case report that we presented in the *European Respiratory Journal* of a patient with chronic obstructive pulmonary disease (COPD) who experienced respiratory depression after inadvertent opioid overdose while using opioids to manage refractory breathlessness [1].

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As N.T. Vozoris notes, the case patient was first prescribed opioids for refractory breathlessness during a hospital admission with an infective exacerbation; however, the episode of respiratory depression only occurred after discharge from hospital, when the patient was recovering from the exacerbation and thus becoming more "stable". Whilst the initiation of opioids for refractory breathlessness has only been evaluated in clinical trials of stable outpatients [2, 3], observational data suggest that opioids are started in up to 18% of COPD patients around the time of hospital presentations for exacerbations [4]. It seems likely that for some of those patients (including our case patient), opioids were commenced for symptom palliation, when it was unknown if the patient would survive or die during the exacerbation. Similarly, in such settings, when the absolute focus of care is to reduce the distress of a patient who appears to be actively dying from respiratory failure, the opioid regimen recommended by either the respiratory team or palliative care team (as in our case report) may differ from the regimens used in clinical trials or suggested by guidelines.

The issue then arises of how to manage opioid therapy prescribed for breathlessness palliation during a near fatal exacerbation when the patient with end-stage disease does survive and is ready to be discharged home. Should the opioid be ceased or continued? If the opioid is ceased, how will the patient and family feel about this? Will there be concerns that the patient will not cope at home without symptom palliation? However, if the opioid is continued, then the questions remain regarding what regimen and what dose should be given, as it seems likely that the dosing requirements will reduce as the acute exacerbation resolves. Such questions as these are commonly faced by clinicians and highlight the challenges that arise in translating evidence into real-world medicine, particularly when prescribing palliative treatments to patients with an unpredictable disease.

We agree with N.T. Vozoris that whilst opioids have an important role in managing refractory breathlessness in patients with advanced lung disease, the needs, comorbidities and abilities of the patient must be included in the careful evaluation of the risks and benefits of any opioid treatment regimen. Significant adverse events, including inadvertent overdose, may occur at any time; therefore, close supervision and support in the community, coupled with individualised, patient-focussed care, are essential to ensure both effective and safe, optimal management of distressing breathlessness.

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References

1 Politis J, Le B, Smallwood N. Respiratory depression secondary to morphine use in a patient with chronic obstructive pulmonary disease and refractory breathlessness. *Eur Respir J* 2017; 49: 1601858.
2 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.
3 Currow DC, McDonald C, Oaten S, *et al.* Once-daily opioids for chronic dyspnea: a dose increment and pharmacovigilance study. *J Pain Symptom Manage* 2011; 42: 388–399.
4 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.