Adverse respiratory effects of opioids for chronic breathlessness: learning lessons from chronic pain

To the Editor:

Fear of fatal respiratory depression is a major driver limiting opioid prescription for persistent breathlessness in chronic obstructive pulmonary disease (COPD) [1–6], but is this fear warranted? In a recent systematic review and meta-analysis, Verberkt *et al.* [7] did not detect significant or clinically relevant respiratory adverse events associated with opioid treatment for chronic breathlessness in COPD. Rather, they concluded that "clinicians' fears of respiratory obtundation with low-dose opioids seem to be unfounded". Here, we critically evaluate these conclusions.

Firstly, all included studies utilised resting measures of respiratory rate, carbon dioxide or oxygen to detect respiratory compromise. These are poor measures of respiratory depression, due to complex interactions between chemoreception, CO_2 excretion and wakefulness (figure 1). Instead, direct measurement of chemoreflex responses is needed to enable more accurate measurement of respiratory depression [8]. Additionally, resting measures do not encapsulate the important effect that opioids may have on breathing during sleep [9], including central sleep apnoea, hypoventilation and oxygen desaturation. Nocturnal hypoxaemia is common in COPD [10] and is likely to be exacerbated by opioids. As such, polysomnography or overnight pulse oximetry would better assess respiratory risk.

Secondly, the data reviewed were powered for efficacy rather than adverse events. The median sample size of the studies considered was just 15.5 patients, and they were thus underpowered to detect true adverse event rates. While the authors state "Data about respiratory adverse effects of opioids are limited and conflicting", their manuscript pointedly ignores the vast literature on the respiratory effects of opioids from other fields of research.

Therefore, we would like to highlight that the world of opioid analgesia has, in fact, been here before. The parallels are marked between the historic arguments used to justify more opioid usage in the treatment of chronic pain and present arguments for their use in chronic breathlessness. In both cases, there is an implication that overcautious clinicians with undue concern are withholding an effective treatment that could relieve a patient's distress. In each case, conclusions have been drawn from palliative care, where the ethical drive is to relieve suffering above all else. Of particular note, Verberkt *et al.* [7] state "Patients are willing to consider opioid treatment for chronic breathlessness, despite the occurrence of adverse effects […] However, physicians remain reluctant to prescribe opioids for chronic breathlessness, because of fear of adverse clinical outcomes".

With remarkable similarity, the 1986 paper by Portenoy and Foley [11] on opioid use in chronic noncancer pain commented "opioid maintenance therapy can be a safe, salutary and more humane alternative to [other] options […] Enthusiasm for chronic therapy, however, has traditionally been tempered by the […] often-stated risk of psychological dependence after sustained exposure to these drugs."

Following this, in 1997, the American Academy of Pain Medicine published a promotional consensus statement titled "The use of opioids for the treatment of chronic pain" [12]. As a consequence, opioid prescription for nonmalignant chronic pain skyrocketed, paralleled by a rapid increase in opioid deaths [13]. However, we now know that tolerance to analgesia develops more profoundly than the tolerance to respiratory depression [14, 15] and thus, over time, the risks of adverse events increase. To further

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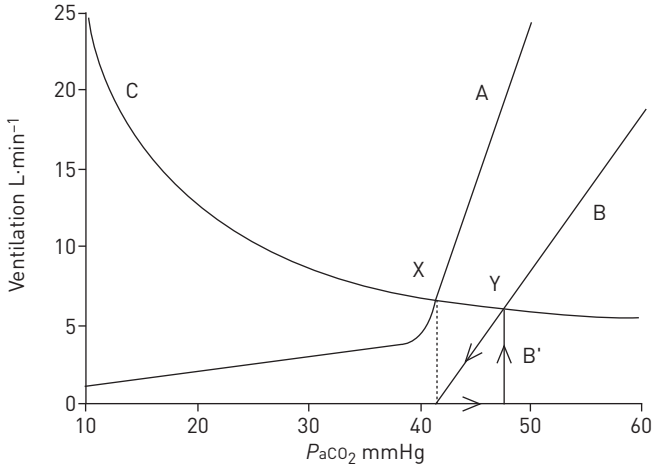

FIGURE 1 This diagram demonstrates how opiates can induce apnoea at the same arterial carbon dioxide tension (P_{aCO_2}) as before opioid administration (dotted line) and also demonstrates that significant reductions in the hypercapnic ventilatory response (HCVR) only cause small changes in steady-state P_{aCO_2}. Curve A represents the normal ventilatory response to CO_2 in an awake individual, demonstrating that ventilation is maintained at very low P_{aCO_2} levels and that apnoea does not occur. Line B represents a 50% depression of the HCVR caused by opioid administration. A notable difference between curve A and line B is that in B, apnoea can occur. Note also that in this case, P_{aCO_2} must rise to steady-state values (*i.e.* along the *x*-axis) for breathing to recommence (line B′). Curve C represents the CO_2 excretion hyperbola and demonstrates how changes in ventilation affect P_{aCO_2}. Point X represents the awake state and point Y represents opioid-depressed breathing. Despite a 50% depression of the HCVR, the CO_2 changes only relatively modestly, illustrating the limited utility of single measurements of CO_2 in assessing respiratory depression. Reproduced and modified from [27] with permission from the publisher.

compound matters, patients with higher levels of anxiety and depression (ubiquitous in both chronic pain and chronic breathlessness) are more likely to respond poorly to opioid therapy, are more likely to require dose escalation and have more difficulties weaning from opioid therapy [16–18]: the perfect storm for increased respiratory adverse events.

There are indeed important differences between patients with chronic pain and those with COPD. Despite increased neural motor output driving respiratory muscles in COPD [19], effective ventilatory responses to hypercapnia (increased arterial CO_2) and hypoxia are blunted due to neuromechanical dissociation [20, 21]. Therefore, opioids may even further obtund ventilatory responses and exacerbate hypoventilation in these individuals. Although we do not know of any work that has studied this in detail, it is interesting to note that COPD is, in fact, a known risk factor for opioid-induced respiratory depression following surgery [22].

Finally, with all of this said, we must consider whether prescribing maintenance opioids for chronic breathlessness is even worth the risk. Although opioids are efficacious for the treatment of acute pain, there is little evidence that they are helpful for chronic pain beyond 3 months [23]. Longer-term studies have found worsened outcomes in terms of quality of life, depression and pain, and significant increases in all-cause mortality [24]. While no studies exist beyond 3 months in breathlessness, based on the history books, we might be able to hazard a guess as to the likely outcomes.

So where do we go from here? Large numbers of people with COPD already receive opioids for pain relief [25] and thus provide an ideal population in whom we can better understand the pharmacodynamics of opioids. Basic physiological studies could help to understand how opioids influence respiratory control in COPD, while sleep studies are needed to investigate whether opioids cause (or worsen) sleep disordered breathing more prominently in COPD than health. Such work would help avoid subjecting large numbers of opioid-naïve people with COPD to novel prospective trials powered for adverse events. Based upon current knowledge, we would even question the ethics of performing such a trial in a population who already have compromised respiration.

And thus, to answer our original question, we believe that fear of adverse respiratory events is still warranted. The opioid epidemic surrounding the over-prescription, drug misuse and the rising tide of deaths [17], has proved a chastening experience for pain physicians. It would be negligent for the respiratory community to ignore those lessons. As noted by Mark Sullivan, a professor of psychiatry and pain in Seattle [26], "The US has conducted an experiment of population-wide treatment of chronic pain with long-term opioid therapy. The benefits have been hard to demonstrate, but the harms are now well demonstrated."

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