



LETTERS TO THE EDITOR

Debating pharmacological options for dyspnoea relief; the need for full, accurate and balanced critical appraisal of the evidence



To the editor,

We read with interest the review on strategies to relieve dyspnoea in patients with advanced chronic respiratory disease by Ambrosino and Fracchia.¹ Given the clinical need for pharmacological options for dyspnoea relief, we would like to comment on some important aspects that we feel merit further clarification.

The review comments on inhaled furosemide as a potential drug for relieving dyspnoea and refers to our RCT in healthy volunteers² which showed significant relief of experimentally-induced air hunger. The review stipulates that this was “a finding not confirmed later even at higher doses.”³ The comment is misleading, implying that higher-dose studies were completed subsequent to ours and that the findings were incongruous. Our study² was published *after* the higher-dose studies. The controlled delivery of 80mg was associated with greater air hunger relief³ compared to what we found with uncontrolled delivery of 40mg (mean ± SE: -17 ± 3 versus $-11 \pm 5\%$ VAS). However, the greater relief in the higher-dose study was offset by a larger placebo effect (-13 ± 4 versus $-2.5 \pm 4\%$ VAS). The enhanced placebo effect in the higher-dose study can be explained by differences in study design.

While there is high variability in dyspnoea relief in all published studies of inhaled furosemide, there is potential for it to form a viable treatment option for the most unpleasant form of dyspnoea if the sources of variability are unravelled. Potential sources of variability include, i) site of drug deposition in the lungs ii) rate of extinction from the lungs iii) lack of information on the quality of dyspnoea rated and iv) use of a dyspnoea model that is not focussed on ‘air hunger’. More research with inhaled furosemide is justified given that it is safe, inexpensive and underpinned by a defined physiological mechanism of action.

The discussion by Ambrosino and Fracchia on the use of opioids for dyspnoea relief is also misleading and fails to paint a balanced picture. The authors have ignored the opioid crisis that has killed over ¾ million Americans since 1999.⁴ They have not considered the absence of long-term studies of opioid efficacy or safety.⁵ In most people, opioid efficacy is high in the short term but diminishes over 6 weeks

to 3 months. The resultant dose escalation increases risk of adverse events with no improvement in symptoms.⁵ We suggest extreme caution is necessary for prescription of opioid medication for breathlessness because, i) opioids increase risk for death in people with lung conditions,⁴ ii) people with anxiety/depression are more likely to have diminished opioid response to pain,⁵ and breathlessness,⁶ but also are more likely to have problems with dependency and failure to wean off opioids.

Finally the author’s assertion that “*Relief of dyspnoea [...] is a human right*” echoes sentiments expressed in the mid 1980’s that were used to justify using opioids for all kinds of pain,⁷ leading to the opioid crisis we are in today. It is preposterous to portray those who harbour legitimate concerns about opioid safety as human rights violators when the debate is not fuelled by a balanced appraisal of the evidence.

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Conflict of interest

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Strategies to relieve dyspnoea in patients with advanced chronic respiratory diseases. A narrative review. Authors' reply



"I speak not to disprove what Brutus spoke, But here I am to speak what I do know".¹

We thank Grogono et al.² for their interest in our review on management of dyspnoea in patients with **advanced** respiratory diseases.³ Breathlessness requires much more attention by clinicians and researchers, as a major health problem around the world for millions of people⁴ and their letter may contribute to the discussion.

Inhaled furosemide. Grogono et al.² give more details of their study in normal volunteers⁵ as well as of other studies. We fully agree with their conclusion that *"More research with inhaled furosemide is justified"*. That's why in our review we concluded that *"based on available data, its (nebulised furosemide...) use for the routine management of dyspnoea in terminal patients is still either controversial or not indicated."* Indeed we are unaware of any guideline recommending the use of inhaled furosemide in patients with **advanced** respiratory diseases.

Opioids. Practitioners and researchers have paid greater attention to management of pain than dyspnoea, and patients with **end-stage** respiratory diseases are less likely to undergo palliative care than patients with cancer.⁶⁻⁸ The controversy on the use of opioids in respiratory diseases is long standing, and we *don't disprove what anyone spoke, we just speak what we do know*. Evidence based international guidelines recommend the use of opioids in *appropriate* doses, *formulations and schedules of administration* in patients with **advanced** chronic respiratory diseases,^{9,10} but

we understand authors' concern about potential long-term adverse effects, lack of effectiveness or risk of addiction. However, we described evidence based management of patients with **advanced** or **end-stage** respiratory diseases with poor short-term prognosis and life expectancy which would be probably not long enough to develop such potential long-term side effects.

Nobody denies that respiratory depression is a predictable adverse effect from a significant opioid *overdose*, while we need further clinical trials to better individualize treatment. Grogono et al.² blame us for ignoring the *"opioid crisis"* quoting a paper¹¹ on *"Opioid Overdose"* induced by illegal use or pain killers and not including *even once* the words *"dyspnea"* or breathlessness: *Overdose* in medicine means malpractice and this is not the case of guidelines. Illegal use or painkillers do not refer to the issue of our review.³ As a matter of fact our review³ underlined the *"need to be aware of and treat adverse effects"* while suggesting a therapeutic escalation exploiting all available pharmacological and non pharmacological tools described in the review.

Finally nobody portrayed *"those who harbour legitimate concerns about opioid safety as human rights violators"*, but we do think that avoiding *all* unpleasant and distressful symptoms, not only pain, in **terminal** conditions **IS** a human right. Whoever has treated or even only seen an **end-stage** dyspnoeic patient with pulmonary fibrosis asking for help, knows what we are talking about.

In conclusion Grogono et al.² criticize us for lack of *"full, accurate and balanced critical appraisal of the evidence"* just because they disagree with some of our evidence based ideas (or what they attribute to us) but we could not agree more with their recommendation. In our (unfortunately...) long life as researchers and clinicians we have always applied that principle, as is the case of this review,³ however in all scientific controversies with our peers we have