Article details	
Title	Initiating Opioids for Refractory Dyspnea in Patients with Advanced Chronic Obstructive Pulmonary Disease: A mixed-methods approach to understanding Patients' Experiences and Outcomes
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Reviewer 1	Prof. Scott A Murray
Institution	University of Edinburgh, Edinburgh, Scotland
General comments	This is a very clearly written multi-centred mixed methods study to understand patients' experiences when opioids are gradually added to optimised conventional treatment for COPD. Its originality and most important factor is that patients' experiences are captured through in-depth qualitative interviews as well as a batch of health related quality of life instruments. It is noted that 73% of the 44 patients completed the trial with 90% reporting it as very or somewhat helpful. Thematic analysis of the qualitative data are gathered around: 1) small gains beget big impact, 2) realigning expectations and 3) "let's try it, there's nothing to lose". The side effects were minimal and most of the quality of life instruments appeared to improve. They thus correctly conclude that opioids were found helpful and acceptable by most patients in their sample with advanced COPD. It is of course noted that people who were unwilling to take part in the study i.e. unwilling to consider opioids were not included. This is a useful addition to the literature as it does, I would think, in most generalists' eyes support the recent professional society recommendations to consider prescribing opioids in this setting. This is a well evaluated (using qualitative interviews and the most relevant QOL tools) intervention. The layout of the analysis of the qualitative data in table 6a is very helpful and gives an indication of frequency of the issues. Methodologically this feasibility study has been evaluated using longitudinal qualitative methods with serial interviews and I believe this is a welcome innovation in understanding and creating complex interventions. Tables 6-8 very usefully summarise the issues that patients found rather problematic including side effects, and the interview guides appear credible at the various stages when asked. In summary, I found this a very useful and relevant mixed methods piece of research. I consider it likely that the benefit would have been 1) due to the therapeutic effects of morphine 2) also due to the great care and monitoring of the patient and 3) also due to a placebo effect of the medication itself. The in-depth qualitative interviews done three times would entail listening with the person and thus be therapeutic. It will be interesting to consider an editorial or discussion about this point at the end of the paper. The question that primary care doctors might have after reading it is "might they be a similar benefit to patients with heart failure"?
Reviewer 2	Morrison, Sean
Institution	Palliative Medicine, Mount Sinai Hospital, New York, New York
General comments	Thank you for the opportunity to review this clearly written, concise, and very interesting manuscript. Treatment of intractable dyspnea is a significant health care issue both in respirology and palliative care. Despite its considerable impact on health and well-being, effective treatments are not widely available. Although opioids have been recommended by professional societies, the evidence supporting these recommendations is sparse and opioids, with the exception of within palliative care and hospice programs, are rarely utilized for this condition. This study makes several valuable contributions to the literature. First, it addresses widely held beliefs among practicing clinicians that the side effects of opioids outweigh their benefit in this setting and that opioids are potentially harmful. The fact that 73% of participants completed the trial without major side effects and that patient interviews (and quantitative data) support their safety and potential efficacy in this disease. Second, the data address the misconception that patients are not amenable to this treatment regimen because of opio-phobia. Third, the study provides strong support and evidence for the safety of an controlled clinical trial. The authors note the limitations of the absence of a control group and the potential of a placebo effect. These are real limitations to the study and as such, should perhaps be highlighted more so than is currently written. Overall, however, this is a rigorously designed mixed-methods study that provides important data to advance the treatment of this serious illness and

	provides strong support for subsequent clinical trials using the innovative dosing and side effect management protocols employed in this study. I have a few additional minor comments below: Page 5, line 22: Can the authors provide details as to the number of patients approached for consent who refused to enroll? Are they able to provide any details as to differences between those that consented and those that refused. Box 1: For those patients that withdrew because of lack of benefit. Did the patient, their doctor, or their primary care provider make this decision? Although the numbers are small, did the investigators observe any pattern in attrition – for example, were older patients less able to tolerate opioids than younger patients? Table 1: Could the authors clarify how they handled nocturnal dosing. Were patients awakened to take a q 4 hour dose or was nocturnal morphine use prn. Similarly, given that the half-life of hydropmorphone is typically shorter than that of morphine sulfate, was the dosing interval shortened to q 3 hours for those who received hydropmorphone? If not, did the investigators observe any treatment related failures at the end of the dosing interval in this group? Box 2: It is somewhat surprising – particularly given the age of the sample that so few of the subjects noted complaints of either cognitive side effects (predominantly mental clouding, sedation) or treatment limiting nausea. Did patients in the study receive treatment for these complications (for example psychostimulants, antiemetics) that allowed them to continue or do the authors believe that the very slow titration schedule – much slower than what is typically used in the treatment of pain resulted in early tolerance for to these side effects obviating the need for active management? This is a notable finding of this study and is perhaps worthy of comment in the discussion Box 6: The waning of effect is slightly troublesome and perhaps suggests the presence of a placebo effect. This obviously could be and should be evaluated in a clinical trial that these data support. Could the authors comment further on this in their discussion? Page 18, line 31. The authors report significant reductions in dyspnea scores. Although the main focus of this paper is on the qualitative results, it would be helpful if the investigators could interpret for readers whether the quantitative reductions in dyspnea scores are clinical meaningful as many CMAJ readers may not be familiar with these scales.
Reviewer 3	McIvor, RA
Institution	Medicine, McMaster University, Hamilton, Ont.
General comments	Excellent team of researchers with expertise in this area. Very well done study although small sample size and significant drop out rate. Well written and presented study It adds to literature but remains "individualized" treatment.
Reviewer 4	James Downar
Institution	University of Toronto, Toronto, Ont.
General comments	Reviewer's Self-Perceived Bias: I frequently prescribe opioids to patients with end-stage COPD and other respiratory illnesses, and I find them very effective and underappreciated. I praise the merits of opioids to anyone who will listen, and am eager to see more literature that highlights their safety and efficacy. Major Comments: This is an excellent research question, and in many ways a difficult area to study. The primary importance of this work is that it demonstrates safety and a strong patient willingness to continue taking opioids once they have tried them. I have 2 major concerns with the manuscript: the structure of the qualitative analysis and the potential for a placebo effect.

	Minor Comments: 1. The flow diagram is provided but I didn't see it referenced in the text. Attrition is well-covered in Box 1. This will be important for skeptical readers. 2. A selected cohort may be problematic in an open label trial with subjective endpoints. The authors mention that they considered the potential placebo effect in their sample calculation, but they did not explain how. Since this was a single-arm study the solution is not obvious to me. The authors also assert that the placebo effect would be "sufficiently" counteracted by the fears of the opioid. I'm not aware of any empirical basis to make such a statement. I am concerned about a placebo effect in this study because of the remarkable improvements in the QOL metrics by 2 weeks, without any apparent side effects. In fact, many of the common side-effects of opioids (nausea, dry mouth) actually became less common after starting the opioid, which is puzzling. The timeframe is important because the titration schedule is extremely conservative. This is not meant to be a criticism because the stated purpose of the protocol was safety and trust-building, which are important in this population. However, it is hard to imagine how these low doses of morphine (e.g. 6mg total daily dose at day #7, which is the equivalent of 2 Tylenol #3s in a 24-hour period), could produce such remarkable improvements so quickly. I would suggest acknowledging the potential for placebo and nocebo effects, and the need for RCTs to help tease them out. I would also suggest that the authors acknowledge that the lack of side effects does raise greater suspicion for a placebo effect. 3. The mixed methods approach is a good one, and provides depth to the quantitative data. 4. The axial structure of the qualitative analysis is a little confusing. The authors begin by stating that the themes "Small gains/big impact", "ongoing realignment of expectations" and "Try it" all lie within the experience of "benefit over burden". However, within the small gains/big impact theme is a subtheme also labeled "benefit over burden". Could this term be changed to something else to avoid confusion? I'm also confused by the theme "realigning expectations" to cover the sub-themes "disappointment", "burden exceeded benefit", and "uncertainty". The first two themes are essentially negative or speak about preferences for pills over liquid, and the quotes don't really touch on expectations at all. The "uncertainty" theme is also a bit of a grab-bag of quotes that range from fears to specific requests for smaller doses, but they do not typify "uncertainty" in my mind. I am conscious of the fact that I have not seen all of the data, and so these labels and structure may be appropriate but I cannot see this from the data presented. I would suggest either different quotes, or a different axial structure with different labels. 5. Safety is a major concern for skeptical readers, and so I am glad that the authors highlighted a low mortality rate and non-excessive hospitalization rate. 6. Among the lessons learned, the authors note that each patient was an n=1 study. I definitely agree with this statement, but I was disappointed that the authors did not study those who "failed" to show benefit from opioids or chose to stop them, to see if there were any common themes (gender, comorbidity, doses). 7. The limitations should also acknowledge the fact that 20% of patients withdrew principally because they did not derive benefit or had serious side effects. These patients were not included in the subsequent CRQ, CRQ-D, and NRS scores, which may have led to an overestimation of benefit simply by attrition. 8. Table 6a shows 40 patients completing a survey at 4-6 months, 38 of whom show a clear preference to continue opioids. However, there were only 32 patients in the trial at this point according to the flow diagram. Can you please resolve this discrepancy. 9. Was the sustained-release morphine a 12-hour sustained release (M-eslon, MS-Contin) or 24-hour (Kadian)? I am assuming 12-hour release since the 15mg dose is mentioned, but this should be specified.

	10. Do you have any data on the baseline pCO2 or O2 saturations of your cohort? I have occasionally had push-back from respirologists who feel that hypoxemic or hypercarbic patients have not been studied sufficiently in the literature to establish safety.