OPIOIDS IN COPD: A "CRISIS" FOR RESPIROLOGISTS
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Introduction
Canada has the second highest per capita opioid prescribing rate in the world.\textsuperscript{1} Over the past two decades in Ontario, as prescription opioid use has increased, opioid-related deaths have doubled.\textsuperscript{2} The devastating consequences of prescription opioid over-use in the general population has been highlighted in the media for some time.\textsuperscript{3} In response to the concerning trends in opioid use and adverse events, a variety of policies and programmes have emerged designed to optimize physicians’ opioid prescribing practices, including the publication of updated national opioid prescribing guidelines for chronic non-cancer pain\textsuperscript{4} and the implementation of the Narcotics Awareness and Safety Act in November 2011 in Ontario.\textsuperscript{5}

However, a somewhat paradoxical message relating to opioids has concurrently emerged in the area of chronic obstructive pulmonary disease (COPD) management. While several policies and programmes have encouraged the more judicious use of opioids in the general population, several recent respiratory guidelines,\textsuperscript{6-9} including one from the Canadian Thoracic Society,\textsuperscript{6} express support for using opioids for difficult-to-control dyspnea in advanced COPD. Without question, opioids are an important tool in the care of individuals with COPD, who are at end-of-life, by helping to reduce intolerable suffering related to dyspnea and pain. However, there are also many individuals with COPD troubled by ongoing respiratory symptoms despite maximization of conventional therapy, but who are not end-of-life in the strictest sense of the term. The respirologist may understandably struggle with opioid prescribing in this setting, weighing the potential for symptom benefit against the potential for adverse effect, and considering recommendations from respiratory guidelines versus messaging coming from media and government.

In this review, data on the scope and pattern of opioid use in the COPD population will be presented. Evidence in support of opioids for the management of refractory dyspnea in COPD will be discussed and critically analyzed. Recently published safety studies examining for possible opioid-related respiratory harms in COPD will be presented. Finally, COPD guideline recommendations relating to opioids will be critically examined in light of the current evidence.
Patterns of Prescription Opioid Use Among Individuals With COPD

Consistent with trends in the general population, opioids appear to be used frequently, and in other potentially concerning ways, among individuals with COPD. One population-based study from Sweden found prevalent opioid use between 2005-2009 to be 50% among individuals with oxygen-dependent COPD. Furthermore, about 60% of Swedes with advanced COPD receiving opioids were on relatively high doses of >30 mg oral morphine equivalents per day. A second population-based study from Ontario found that about 70% of individuals with non-palliative COPD, ages 66 years and older, received a new opioid drug between 2003-2012. New opioid use was also found to be increasing over time among older adult Ontarians with COPD. Besides opioids being commonly and increasingly used among older adult Ontarians with COPD, other potentially concerning patterns of opioid use were noted in this population, including multiple opioid dispensings on the same day, prolonged durations of use, repeat prescriptions and early refills. About 15-20% of new opioid dispensings among older adult Ontarians with COPD were also found to be given around the time of an acute respiratory exacerbation and Canadian Thoracic Society guidelines explicitly state that opioids should only be used in the setting of "stable COPD". Opioids appear to be used also with increased frequency among certain subgroups of Ontarians with COPD that would be at higher risk for experiencing adverse drug-related events, including concurrent recipients of benzodiazepine drugs, individuals with comorbid cardiovascular disease and individuals with comorbid sleep disorders. The source of the vast majority of opioid dispensings among individuals with COPD is primary care physicians.

While one may assume that when opioids are prescribed among individuals with COPD they are largely intended for the management of dyspnea, there is evidence to support that this is not in fact the case. Similar to the general population, opioids in the setting of COPD are largely used to treat musculoskeletal pain. Chronic musculoskeletal pain has been estimated to occur in over 70% of individuals with COPD. Several factors likely contribute to the high frequency of musculoskeletal pain observed in COPD: muscle weakness and wasting from decreased mobility due to breathlessness; respiratory muscle overload and fatigue from altered breathing patterns; osteoporosis; and, skeletal muscle changes as a result of hypoxemia and systemic inflammation. In Ontario, close to 90% of opioids dispensed to older adults with COPD were those opioids that were combined with acetaminophen or aspirin in a single product. Such combination opioid/non-opioid products are unlikely to be used in the management of refractory dyspnea and are instead more likely prescribed to treat pain. Opioids are also more frequently prescribed to non-exacerbators versus exacerbators in Ontario, which again supports the premise that opioids are often prescribed in COPD for reasons other than palliation of respiratory symptoms. In Sweden, where information on prescribing indication is incorporated in health administrative drug dispensing databases, 97% of opioid use among individuals with advanced COPD was found to be for pain control and only 2% was for the management of breathlessness. The latter finding suggests a potential under-use of opioids for dyspnea control among individuals with an advanced degree of COPD. While overall opioid use in the COPD population is frequent, several studies at the same time have documented
reluctance among physicians to prescribe opioids for refractory breathlessness in advanced COPD.\textsuperscript{15-17} However, one study using information relating to over 200 individuals that died from COPD found that breathlessness was in fact more frequently and effectively treated than pain in the last year of life.\textsuperscript{14}

**Critical Appraisal of the Evidence in Support of Opioids For the Management of Dyspnea in COPD**

In 2015, Ekstrom et al.\textsuperscript{18} published an updated, systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials of opioid therapy for breathlessness and exercise capacity in advanced COPD. Eight trials involving systemic opioids (with 118 study participants in total) were included in the analysis.\textsuperscript{18} The intervention arm in most trials consisted of a short-acting opioid for a few days. In the pooled analysis of all studies, opioids significantly improved dyspnea scores compared to placebo (standard mean difference [SMD] -0.34; 95% confidence interval [CI] -0.58 to -0.10).\textsuperscript{18} However, a closer look at the pooled analysis reveals that only two of the eight studies demonstrated a significant positive effect for opioids for breathlessness, and these two studies were weighted relatively more heavily than the remaining six, which showed no significant benefit of opioids over placebo.\textsuperscript{18}

The magnitude of effect of opioids on dyspnea in the two positive trials in the Ekstrom et al. review\textsuperscript{18} deserves further scrutiny. One of the positive trials was by Abernathy et al.,\textsuperscript{19} a randomized, double-blind, placebo-controlled crossover trial of sustained release oral morphine 20 mg for four days in 42 participants (88% of whom had COPD and 12% of whom did not have COPD). The primary outcome was morning and evening sensation of dyspnea, measured on a visual analogue scale from 0-100 mm. When receiving morphine compared to placebo, participants reported improved dyspnea scores, specifically, morning scores were 6.6 out of 100 mm better (95% CI 1.6-11.6 mm) and evening scores were 9.5 out of 100 mm better (95% CI 3.0-16.1 mm).\textsuperscript{19} While these results were statistically significant, a less than 10 point improvement out of 100 on a visual analogue scale falls below what is considered to be a minimum clinically important difference (a 10-20 mm change is considered to be minimally clinically important).\textsuperscript{20} Even the authors acknowledged the uncertain clinical significance of their results in their discussion.\textsuperscript{19} Secondary efficacy outcome measures in the trial included self-reported sleep disturbance by dyspnea, exercise tolerance as per the modified Medical Research Council (mMRC) scale and overall sense of well-being, and mixed results were observed.\textsuperscript{19} While significantly fewer participants reported sleep disturbance by breathlessness when receiving opioid over placebo, mMRC score and overall sense of well-being were not significantly different.\textsuperscript{19} The second positive opioid-dyspnea trial was by Johnson et al.,\textsuperscript{21} a randomized, double-blind, placebo-controlled crossover trial of dihydrocodeine 15 mg up to three times daily for one week in 18 patients with advanced COPD. Breathlessness was measured on a 0-10 cm visual analogue scale and the mean difference in dyspnea score between the treatment and the placebo was only 1.0 cm.\textsuperscript{21} While the minimum clinically important difference on 0-10 cm visual analogue scale is not known, given what is felt to be a minimally clinically meaningful difference on the 0-100 mm visual analogue scale and on the 0-10 Borg scale,\textsuperscript{20} this result is likely below or just at a clinically significant threshold.
Furthermore, opioid-related beneficial effects were observed in only a limited number of study participants, as over half reported a difference in breathlessness score of < 1.0 cm with the opioid.21

In the pooled analysis of trials in the Ekstrom et al. review,18 opioids were observed to overall result in no improvement in exercise capacity in advanced COPD (SMD 0.06; 95% CI -0.15 to 0.28).18 This finding again raises questions about the clinical significance of the small improvements in dyspnea intensity using opioids that have been demonstrated in a few trials. It should be noted that one of the eight trials included in the Ekstrom et al. review showed statistically significant, and likely clinically-meaningful improvements, in exercise capacity with opioids. Compared to placebo, Johnson et al.21 reported that opioids resulted in a 1.6 km increase in walking distance per week and a 36 m increase in walking on a 30-minute incremental exercise treadmill test. Following publication of Ekstrom et al.’s meta-analysis,18 Abdallah et al.22 reported the results of a randomised, double-blind, placebo-controlled, crossover trial of single-dose, immediate-release morphine (given at a dose of 0.1 mg/kg, up to a maximum of 10 mg) on cardiopulmonary cycle exercise testing outcomes in 20 individuals with advanced COPD. Compared to placebo, morphine reduced exertional breathlessness by 1.2 Borg units at isotime22 (with a 1.0 point change in Borg score being considered a minimum clinically important difference20) and increased exercise endurance time by 2.5 minutes22 (with about a 1.7 minute change being considered a minimum clinically important difference23). However, opioid-related beneficial effects were observed in only about half of the study participants.22

Another important feature to consider when interpreting trials of opioid efficacy in advanced COPD is study external generalizability. All the clinical trials included in the meta-analysis by Ekstrom et al.,18 as well as the one by Abdallah et al.,22 excluded most, if not all, of the following groups of individuals: those with a history of acute respiratory exacerbation; those with hypercapnia; individuals with comorbid cardiovascular or neuropsychiatric disease; and, recipients of other sedating medications. However, these clinical characteristics are frequently encountered among individuals with advanced COPD. For example, it is estimated that 90% of individuals with COPD with moderate-to-severe airflow reduction have acute respiratory exacerbations.24 Half or more of individuals with COPD are estimated to have at least one cardiovascular comorbidity.25 An estimated 40% of individuals with COPD experiencing respiratory exacerbations are recipients of benzodiazepines.26

In summary, while there is some supportive evidence for using opioids in advanced COPD to reduce refractory breathlessness and improve exercise tolerance, there are outstanding questions relating to the magnitude and generalizability of possible beneficial effects.

**Evidence of Respiratory Harm Associated With Opioid Use in COPD**

Thus far, randomized clinical trials of opioid efficacy in COPD invariably report few-to-no clinically-important, adverse respiratory side-effects (like acute respiratory exacerbation, respiratory depression or respiratory-related death).18 However, these clinical trials are ill-suited to adequately evaluate for possible opioid-related respiratory harms for several reasons:
small numbers of study participants were generally included (usually in the range of 10-20 participants per study); individuals at-risk for adverse respiratory effects were invariably excluded from participating (such as, exacerbators, hypoventilators, those with comorbid illnesses and individuals with previous adverse reactions to opioids); and, low or single-dose opioid regimens were usually evaluated, which are not reflective of real-world drug usage. A recent systematic review and meta-analysis stated that there is "no evidence of significant or clinically relevant respiratory adverse effects of opioids for chronic breathlessness". However, only clinical trials of opioid efficacy were included in this meta-analysis (and such studies are not designed to properly evaluate for possible drug harms) and most of the outcomes reported on in the meta-analysis were physiologic measures (e.g., oxygen saturation, respiratory rate, etc.), of uncertain clinical importance.

Several well-designed observational studies evaluating for the respiratory safety of opioids in the COPD population have been published recently. These studies were characterized by features that made them well-suited to adequately evaluate for issues of possible drug harm: they were based on large sample sizes; individuals from the broader COPD population were included; real-world drug doses and patterns of drug use were captured; there was minimal-to-no loss to follow-up; and, analyses were adjusted for a large number of relevant covariates. Using a prospective cohort design, all-cause hospitalization and all-cause mortality were examined in relation to prevalent opioid use in over 2000 oxygen-dependent Swedes with COPD. After adjusting for an impressive list of covariates (including, but not limited to, World Health Organization [WHO] performance status, forced expiratory volume in one second, arterial blood gas oxygen and carbon dioxide tensions, and smoking status), individuals receiving >30 mg oral morphine equivalents per day compared to non-opioid users had about a 20% significantly increased risk of all-cause mortality. This finding did not extend to recipients of ≤30 mg oral morphine equivalents per day and no association was observed with all-cause hospitalization, regardless of opioid dose. A retrospective cohort study involving ~130,000 non-palliative, community-dwelling, older Ontarians with COPD evaluated for 30-day respiratory-related morbidity and mortality in relation to incident opioid use. In adjusted analyses where 33 relevant covariates were balanced between opioid users and non-users using propensity score methods, incident opioid use was associated with significantly increased ER visits for COPD or pneumonia (hazard ratio [HR] 1.14, 95% CI 1.00-1.29), COPD or pneumonia-related mortality (HR 2.16; 95% CI 1.61-2.88) and all-cause mortality (HR 1.76, 95% CI 1.57-1.98). Respiratory-related morbidity and mortality risks were even greater when opioid-only formulations were considered (i.e., those formulations where the opioid drug was not combined with a non-opioid agent, like acetaminophen or aspirin). In a sensitivity analysis among individuals with less severe COPD (defined as those with no respiratory exacerbation in the preceding year), increased rates of respiratory-related morbidity and mortality were found to persist among opioid users versus non-users, lending further credibility to the overall findings, as this subgroup would be least likely to be influenced by confounding by indication. In further subgroup analyses, users of both short-acting and long-acting opioids, and recipients of both lower-dose and higher-dose opioids, were observed to have significantly increased rates of respiratory-related morbidity and mortality, suggesting that there is no opioid formulation or dose where adverse respiratory events do not occur. Finally, two population-based, case-
control studies reported that opioid use was associated with significantly increased risk of objectively-confirmed pneumonia.\textsuperscript{30-31} Although these two studies were not specifically undertaken among individuals with COPD, the exposure (i.e., opioid drugs) and the outcome (i.e., pneumonia) examined makes their inclusion in this present review appropriate and relevant. Pneumonia risk was observed to increase with escalating opioid dose, potency and recency of use,\textsuperscript{31} further supporting the likelihood of a causal link between opioids and respiratory harm.

In summary, several properly-designed safety studies demonstrate that opioids are associated with increased risk for respiratory harm in COPD. While these studies are not able to establish a causal relationship between opioids and adverse respiratory outcomes, and while not every individual with COPD who receives an opioid will have an adverse event, there is supportive evidence that risk for respiratory harm should be taken into consideration in opioid prescribing decision-making in COPD.

COPD Guideline Opioid Recommendations in the Context of Current Evidence
In 2011, the Canadian Thoracic Society published a clinical practice guideline regarding the management of dyspnea in advanced COPD.\textsuperscript{6} One of the published recommendations was: "We recommend that oral (but not nebulized) opioids be used for the treatment of refractory dyspnea in the individual patient with advanced COPD".\textsuperscript{6} While the wording of the recommendation comes off fairly strong, the guideline authors gave the recommendation a relatively weak grade, in keeping with the results and quality of opioid efficacy studies published up to that time. Specifically, the recommendation was graded as a "2C", which means it was a "weak recommendation, with desirable effects closely balanced with undesirable effects".\textsuperscript{6}

Starting in 2006,\textsuperscript{32} and up until 2016,\textsuperscript{33} the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines presented a fairly balanced position on opioids for refractory breathlessness in advanced COPD, acknowledging that these drugs had dyspnea-relieving potential, while at the same time cautioning against their broad application in COPD.\textsuperscript{33} Specifically, GOLD guidelines stated, "Oral and parenteral opioids are effective for treating dyspnea in COPD patients with advanced disease...However, some clinical studies suggest that morphine used to control dyspnea may have serious adverse effects and its benefits may be limited to a few sensitive subjects".\textsuperscript{33} It is noteworthy that the GOLD guidelines cautioned regarding clinically important adverse effects in association with opioid use as far back as 2006, even though many of the opioid safety studies in COPD did not appear in publication until much later.

However, 2017\textsuperscript{34} and 2018\textsuperscript{9} GOLD guideline recommendations on opioids for refractory breathlessness in advanced COPD markedly depart from what was written in earlier versions. Similar to previous,\textsuperscript{32-33} the newer versions of the GOLD guidelines state that opioids can be effective for refractory breathlessness, but now go on to encourage "wider use of palliative therapies that in the past have often been restricted to end-of-life situations".\textsuperscript{9,34} Comments on opioid-related adverse effects and the generalizability of opioid-related benefits, which were
present in earlier versions of the guidelines, are now absent, even though there is evidence from randomized clinical trials and drug safety studies supporting both of these concepts. Indeed, it is odd that the recent GOLD guidelines encourage a more liberal use of opioids in COPD, in spite of mounting evidence to support the opposite approach, given that opioids are over-used in the COPD population and that use of this drug class is associated with heightened risk of serious adverse respiratory outcomes.

**Conclusion**

Similar to general population trends, opioids appear to be over-used among individuals with COPD and musculoskeletal pain (not dyspnea) is the main reason for drug receipt. This pattern of medication use is concerning, given that several drug safety studies have demonstrated that opioids are associated with increased risk for adverse respiratory events among individuals with COPD, including acute respiratory exacerbations and respiratory-related death. Several drug safety studies also show that there is no opioid dose, potency or half-life formulation at which adverse respiratory-related outcomes do not occur. Nevertheless, there is some evidence to support that opioids can be effective at reducing refractory breathlessness in COPD and the door on this therapeutic strategy should not be fully closed. However, the magnitude of possible benefit, and which individuals with advanced COPD are likely to improve with opioids, are areas of some uncertainty. Younger individuals and individuals with greater breathlessness intensity may be groups that are more likely to respond to opioid therapy, but further research to try and identify opioid responders and optimal opioid regimens is needed. In contrast to what is recommended in some COPD guidelines, current evidence does not support the broad use of opioids for the management of refractory breathlessness, and instead, caution should be exercised when prescribing opioids in the individual COPD patient.

**References**


