Special Article

Gaps in the Evidence Base of Opioids for Refractory Breathlessness. A Future Work Plan?

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Abstract

Breathlessness or "shortness of breath," medically termed dyspnea, remains a devastating problem for many people and those who care for them. As a treatment intervention, administration of opioids to relieve breathlessness is an area where progress has been made with the development of an evidence base. As evidence in support of opioids has accumulated, so has our collective understanding about trial methodology, research collaboration, and infrastructure that is crucial to generate reliable research results for palliative care clinical settings. Analysis of achievements to date and what it takes to accomplish these studies provides important insights into knowledge gaps needing further research and practical insight into design of pharmacological and nonpharmacological intervention trials in breathlessness and palliative care. This article presents the current understanding of opioids for treating breathlessness, what is still unknown as priorities for future research, and highlights methodological issues for consideration in planned studies. J Pain Symptom Manage 2012;43:614–624. *© 2012 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words

Palliative care, opioid, dyspnea, research

Introduction

Breathlessness or "shortness of breath," medically termed dyspnea, remains a devastating problem for many people and those who care for them. It is frequently dismissed by both those that suffer from it as an inevitable part of growing older or as self-induced, and by clinicians who consider it intractable. Thus, the symptom has been described as "invisible."[1] However, the past decade has seen progress with regard to understanding the link between pathophysiology and the genesis of breathlessness, pharmacological treatments, and nonpharmacological interventions.

Several motivating factors have contributed to the current interest in breathlessness, both

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Accepted for publication: April 27, 2011.

0885-3924/$ - see front matter
doi:10.1016/j.jpainsymman.2011.04.024

clinically and in research. First, chronic obstructive pulmonary disease (COPD) research has increasingly focused on symptoms and symptom improvement, largely because treatments that lead to improvement in survival are few. Secondly, there has been inequitable access to palliative care services for people with nonmalignant diseases as highlighted by powerful patient voices describing their experience and the impact of the symptom on the realities of daily living,[1–4] and comparable symptom burden.[5–9] Thirdly, breathlessness has been described as "the pain of nonmalignant disease;" the conceptual similarities between pain and breathlessness, the "total" experience affecting all domains of life, and the pathophysiology of the symptoms and their response to treatment are remarkably similar, with observations supported by neuroimaging and clinical studies.[10,11]

People at the end of life want to participate in research that will improve the quality of care.[12] As a treatment intervention, administration of opioids to relieve breathlessness is an area where progress has been made. As evidence in support of opioids has accumulated, so has our collective understanding about trial methodology, research collaboration, and the infrastructure that is crucial to generate reliable research results in palliative care clinical settings.[13–15] Methodologically rigorous research is imperative and achievable, so that people, often frail, do not give valuable time to projects that do not meaningfully contribute to the evidence base.[16] It is important that the energy spent is not wasted on failed, underpowered or inadequately designed studies that do not provide the answers vitally needed to inform clinical decision making.

Analysis of achievements to date and what it takes to accomplish these studies provide important insights into evidence gaps needing further research and practical insight into design of pharmacological and nonpharmacological intervention trials in breathlessness and palliative care. This article presents the current understanding of opioids for treating breathlessness, highlighting what is still unknown. Sections explicitly divide the known and the areas for exploration (Table 1);[17–25] however, it is acknowledged that areas with clear evidence are incomplete and that areas described as "unknown" incorporate unfolding insights. Suggestions for study designs required to address remaining questions are presented.

What Do We Know?

Efficacy

A 2002 Cochrane review concluded that regular morphine, diamorphine, and dihydrocodeine improved the sensation of chronic refractory breathlessness by a statistically and clinically significant effect size.[17] An adequately powered, placebo-controlled study of oral morphine published the following year confirmed this finding, improving morning breathlessness intensity by a statistically and clinically significant 6.6 mm and evening breathlessness by 9.5 mm on a 0–100mm visual analogue scale (VAS). This was a 13%–19%

Table 1
Current Knowledge

Areas With Initial Evidence From Rigorously Designed Studies Focusing on Regularly Administered, Low-Dose Opioids to Treat Breathlessness	Areas in Which Further Rigorously Designed Studies Are Needed
1. Efficacy[17–19]	1. Is there a class effect from opioids? Do mu-opioid agonists deliver the most benefit?
2. Effective routes of administration (oral, parenteral)[17]	2. Can we define particular subgroups of people for whom opioids are more beneficial?[25]
3. Safety and tolerability[20]	3. What is the true role of opioids in the relief of breathlessness in clinical practice?
4. Minimal change in efficacy required for patient-defined benefit (minimal clinically important difference)[21,22]	4. What is the role of other routes of administration such as intranasal, buccal, transdermal, or nebulized?
5. Definition of a central mechanism of action[23,24]	5. What other opioid mechanisms help to ameliorate breathlessness?
	6. Are there agents that synergistically enhance the efficacy of opioids?
	7. What are the barriers and facilitators to opioid prescribing in breathlessness?

improvement on the participants' average baseline refractory dyspnea measurement of 50 mm on a 100mm VAS. Participants had a variety of underlying etiologies, mainly COPD.[18] Further systematic reviews in cancer patients only, assessing the efficacy of morphine for breathlessness, have supported the use of oral and parenteral morphine.[26–28]

Effective Routes of Administration (Oral, Parenteral)

The Cochrane review conclusions were related to parenteral or oral administration of regular low-dose opioids that included morphine, diamorphine, or dihydrocodeine but stated there was no current evidence to support the use of nebulized opioids, although studies were short term and under-powered.[17] As such, an adequately designed and executed trial of nebulized opioids is required before a benefit from this form of administration can be excluded.

Since then, there have been several more studies of nebulized opioids (fentanyl, morphine, and hydromorphone),[15,29–33] the results of which follow a pattern according to study design. Randomized studies that measured dyspnea (two with morphine, and one with hydromorphone) had negative findings,[29,32,33] but the small observational cohort of nebulized fentanyl ($n = 35$) showed benefit,[30] as did the single case report.[31] Unfortunately, the placebo-controlled randomized trial of fentanyl failed to recruit.[16] Likewise, case series of intranasal and transmucosal routes of fentanyl administration have shown benefit.[34–36] Given that the genesis of breathlessness is multifactorial, it is not surprising that benefit seen in uncontrolled studies may decline or disappear when trials are blinded and randomized; for example, using "before and after" comparisons can exaggerate treatment effects by 61% compared with controlled studies.[37]

Safety and Tolerability

In a two-stage dose titration (83 participants: 54% COPD; 29% primary lung cancer; 12% interstitial lung disease; 5% other causes) and pharmacovigilance (52 participants) open-label study, opioid-naïve people with multietiology dyspnea were titrated daily from 10 to 30 mg sustained-relief morphine according to clinical benefit and study algorithm.[20] Patients were treated with weekly dose increments until effect and then treated long term on the dose (if any) resulting in clinical benefit. This study provided more than 30 patient-years of data. On an intention-to-treat basis, the response rate at the end of the dose-titration period was 52 (63%) of 83, giving a number needed to treat of 1.6; taking into account unacceptable side effects, the number needed to harm was 4.6. Of those who responded, 93% had done so by a dose of 20 mg daily. In the pharmacovigilance phase, 14 of 52 stopped morphine because of unacceptable side effects, with constipation being the most common reason (six people). There were no episodes of respiratory depression or hospital admissions caused by sustained-release morphine in either phase.

Minimal Change in Efficacy Required for Patient-Defined Benefit (Minimal Clinically Important Difference)

Using calculated mathematical models based on people with chronic breathlessness as a result of COPD, Ries[22] concludes that a minimally clinically important difference (MCID) is a change of one point on the Borg scale and 10–20 mm on a VAS. A consensus statement confirms this recommendation and expands it to cover all etiologies, indicating that a one-point improvement in the Borg score and 10 mm on a VAS is a MCID.[21] Recently, emerging data from a population of heart failure patients with chronic breathlessness have suggested that between 0.5 and 2.0 improvement in a 0–10 numerical rating scale (NRS) is meaningful, equating to a one-point change on the global impression of change in breathlessness scale (unpublished data calculation from S. Oxberry. Thesis: Opioids in Heart Failure, University of York, 2010). MCID in chronic breathlessness is markedly different to the MCID in acute breathlessness. Data demonstrate that for acute breathlessness, an improvement of two on a 0–10 NRS is the MCID and probably reflects the qualitatively different experiences of both situations.[38,39]

Therefore, morphine's impact of approximately one or more on a NRS (10 mm on a VAS) is consistent with calculated and patient-defined MCID for chronic breathlessness.[18,19] Even seemingly small changes identified in the efficacy studies lead to clinically important improvement. However, recommendations

continue to highlight that patient-rated variables should be included in studies to confirm patient-defined clinical impact and how it correlates with differences in dyspnea rating scores (e.g., patient-reported global benefit of the intervention, patient preference for the intervention).

Definition of a Central Mechanism of Action

The mechanisms whereby opioids help the sensation of breathlessness are not fully clarified, but there is progress in our understanding. Opioid receptors and endogenous opioids are found throughout the cardiorespiratory system and endogenous opioid release forms part of the complex neuroendocrine response in heart failure, a syndrome characterized by chronic and acute-on-chronic dyspnea.[40–42] A recent randomized controlled trial in COPD patients showed worse dyspnea after treadmill exercise in those given naloxone (a centrally and peripherally acting opioid antagonist) compared with placebo, confirming that endogenous opioids mediate the sensation of breathlessness.[23] Animal and human studies suggest mechanisms whereby opioids may ease dyspnea. Sympathetic stimulation and endogenous opioid production appear to be interlinked in a complex manner involving both central and peripheral mechanisms. Opioid receptor agonism may inhibit sympathetic drive by reducing intracellular cAMP, in the periphery, where this mechanism has been demonstrated in the myocardium.[43,44] Down-regulation of peripheral chemoceptors also may reduce ventilatory drive and thus reduce sympathetic outflow.[45]

In addition to these mechanisms, neuroimaging study groups are starting to apply the knowledge gained from work with functional magnetic resonance imaging (fMRI) in pain to breathlessness.[11,24,46–50] The integrated cortical and subcortical network found to be involved in the perception of breathlessness induced in normal volunteers is strikingly similar to that involved in the perception of pain, especially within the context of the role of emotion and higher-order cognitive functioning. It has been more challenging to study the functional neuroimaging of people with chronic breathlessness as a result of pathology because it is more difficult for them to tolerate fMRI. However, there is one study of people with chronic asthma that demonstrates some evidence of down-regulation of the anterior insula, the area thought to be integrally related to perception of "unpleasantness."[49] This is in keeping with the smaller MCID for chronic breathlessness than for acute breathlessness, although this study did not apply the same resistive load to patients and normal controls.

In initial work with opioids and fMRI in induced breathlessness in normal volunteers using breath holding as a model of inducing "urge to breathe," Pattinson et al.[24] have shown that remifentanil is able to decrease localized breathhold-related "urge to breathe" activity in the left anterior insula and operculum in conjunction with a corresponding dramatic reduction in the participant's awareness of respiration. Motor and sensory activities, however, were largely unaffected by remifentanil.

What Is There to Find Out?

Is There a Class Effect From Opioids? Do Mu-Opioid Agonists Deliver the Most Benefit?

In general, open-label observational studies of opioids other than morphine are positive, but most of them are very small studies or case series only. The few randomized trials fail to confirm benefit, and well-designed, adequately powered studies are needed to answer this question.

Oxycodone is an interesting opioid in that it has kappa and mu activity. Whether this translates into additional benefit for people with dyspnea, in terms of efficacy or safety, is unknown. There is a double-blind, parallel-arm trial randomizing participants with refractory breathlessness to receive morphine, oxycodone, or placebo to steady-state, open in Australia (ACTRN12609000806268), but more comparative research is needed. In people with New York Heart Association Class III/IV heart failure, an adequately powered comparative crossover study with oxycodone, morphine, and placebo failed to demonstrate any superiority of any intervention in any arm, although breathlessness improved in all, including those in the placebo arm (ISRCTN85268059).[51]

Can We Define Particular Subgroups of People for Whom Opioids Are More Beneficial?

It is clear that not all patients benefit from opioids for chronic breathlessness. The correlation between baseline dyspnea severity and response to opioids was assessed in the study

of 20 mg modified-release morphine daily for refractory breathlessness.[25] This was an exploratory study that was not powered to define predictors of response, but younger age, better performance status, and cardiovascular pathology were cited as worthy of further prospective evaluation in a larger trial. The "dypnea target," a model of opioid responsiveness, has been suggested as a conceptual approach in the selection of patients for opioid treatment as part of their breathlessness management, in an attempt to incorporate factors that may influence opioid responsiveness in an individual, but this has yet to be tested.[52] Clearly, more work is needed to identify patients most likely to benefit from opioids, with the lowest likelihood for toxicity.

The majority of people in the studies described above had breathlessness as a result of COPD or cancer; very few participants had cardiac disease. There is one reported pilot study of repeated-dose morphine in heart failure patients that found a statistically significant improvement in breathlessness in the morphine arm.[19] Although the powered study in chronic heart failure[51] did not show any advantage of opioids over placebo at four days, an open-label, patient-choice, three-month extension study showed improvement in breathlessness in those who chose to continue opioids compared with those who did not. Indeed, those who did not had a slight deterioration in breathlessness severity.

What Is the True Role of Opioids in the Relief of Breathlessness in Clinical Practice?

Apart from the dose-ranging study, the majority of data tells us about efficacy rather than the effectiveness in daily practice. The lack of effectiveness data to support the widespread implementation of opioids into primary, secondary and tertiary clinical practice is perhaps the most dangerous challenge to this body of science, particularly in palliative care and oncology, specialties renowned for their early adopters.[53] There is an urgent need for Phase IV pharmacovigilance comparative studies to give us vital information, not only about the differential effectiveness of various opioids, but also their side effects and impact on daily living when translated into the "real world" of people outside carefully controlled eligibility criteria.

What Is the Role of Other Routes of Administration Such as Intranasal, Buccal, Transdermal, or Nebulized?

There are no studies randomizing participants to receive sustained-release opioids vs. immediately available preparations. We do not know whether transdermal preparations are helpful for breathlessness. We do not know whether patients with stable, predictable breathlessness would gain more benefit from sustained-release preparations, and those with episodic (which could be predictable or unpredictable) breathlessness gain more benefit from newer delivery systems for rapid onset such as transmucosal, buccal, nasal, or inhaled opioids.

What Other Opioid Mechanisms Help to Ameliorate Breathlessness?

As discussed above, the exploration of the mechanisms involved in opioid-induced benefit in terms of both central and peripheral mechanisms is only just beginning. As patients with pathological breathlessness may tolerate fMRI poorly, different methods of investigating brain activity could be explored, such as magnetoencephalography, which does not require the patient to lie flat. Peripheral mechanisms involving the interplay between the sympathetic nervous system and peripheral muscles would be another interesting target for researchers.

Are There Agents That Synergistically Enhance the Efficacy of Opioids?

Evidence regarding combined medicinal and pharmacological plus nonpharmacological interventions that incorporate opioids is generally lacking. There is one study that shows that morphine and midazolam give additional benefit when administered together in dyspneic patients in the dying phase (last hours or days of life), compared with giving midazolam alone.[54] Although morphine alone gave more relief than midazolam alone, the combination was still the more efficacious option. However, before putting this evidence into wider practice, readers should take caution. The study population was very late in their illness and the results are likely more applicable in the last few hours or days of life; for example, approximately 20% of those

randomized died within 24 hours and baseline levels of breathlessness were very severe (>7 on the Borg scale, where 5 represents severe). With the study intervention, improvements were dramatic, with reductions in Borg scores down to 2–3 within 24–48 hours. This study, therefore, highlights another issue in breathlessness research—the participant population needs to be carefully defined, the outcome measure appropriately chosen, and the findings only applied to comparable populations.

A small study ($n = 7$ people with COPD) indicated greater improvement in exercise tolerance with a combination of morphine and promethazine than with placebo or morphine alone, but there was no change in Borg measures of breathlessness.[55]

What Are the Barriers and Facilitators to Opioid Prescribing in Breathlessness?

Compared with the "barriers" work completed in opioids and pain, there is little in breathlessness. There are some data published as conference abstracts.[56,57] Physicians are frequently cautious about prescribing opioids for people with chronic respiratory disease unless they are imminently dying, for fear of respiratory depression or addiction. Consultation with palliative care clinicians appears to help confidence with opioid prescribing.[56] Respiratory therapists in one center found this attitude frustrating as they perceived opioids to be a potentially beneficial intervention. These physician attitudes are not supported by the evidence above but appear to be strongly held in this small selected survey.[56]

Interestingly, one qualitative study reviewed the impact of the Shipman murders on general practitioner prescribing of opioids for COPD in England; the highly publicized murders increased clinician anxiety about prescribing opioids despite evidence to the contrary, and palliative administration decreased.[58] (Note: Harold Shipman was a general practitioner in Northwest England who was sentenced to life imprisonment for the murder of 15 of his patients and of one count of forging a will. The subsequent Shipman Inquiry concluded that he killed approximately 250 patients over 27 years with lethal doses of diamorphine. Concerns were raised in the Inquiry and trial about the regulation of general practitioners in the U.K., particularly in relation to the prescription of opioids.)

Patient barriers are different from physician barriers. In an interview study of men with heart failure from one area of the U.K., polypharmacy and opioid fears would not prevent them from trying opioids, provided they had trust in the prescribing clinician; confidence in their doctor was a strong feature.[59] One patient interviewed commented that his doctor thought that prescribing morphine was dangerous. A strong theme from this study suggested that this group of patients did not associate the use of opioids exclusively with death and dying, in contrast with previous findings in patients with cancer. A possible explanation is that many had had experience of being given morphine very effectively during an acute, frightening, painful, and life-threatening event such as a myocardial infarction, and they seemed to have a much more positive view of it as something to be used if recommended by their clinician. Also, several respondents in the study described experiences of beneficial use of morphine for those they knew with cancer pain, where it resulted in an improved quality of life.

Recommendations for Further Research (Questions and Design)

Much of what we have learned about design from experience with opioid studies can be generalized to dyspnea and palliative care research.

Baseline/Definitional Issues

1. Description of the study population should be routine so that patient profile and setting can be interpreted easily and judgments made with regard to generalizability and applicability of results. Inclusion of ethnicity and socioeconomic status in baseline demographic data collection would be two very helpful measures.
2. Baseline. Definitions of dyspnea, and terms such as "refractory" should be agreed. The operational definition of "refractory dyspnea" has been defined as that which persists even when all identified reversible causes have been treated. This definition has now

been published in several trials, chapters, and opinion pieces and, therefore, we recommend that this be the one used;[18,60–62] importantly, when using the same definition in different studies, similar patient populations were enrolled with respect to intensity of breathlessness, chronicity, and etiology even in different countries. Consistency across trials ensures that studies can be combined and compared.

3. The concept of "total dyspnea" appears to be a useful one and is gaining credence in both clinical and research communities.[10,63] It also seems to have a physiological basis in the perception of breathlessness. This, coupled with the other concept of a "dyspnea target," which also recognizes fear and anxiety as major drivers of breathlessness in subgroups of people, underlines the importance of designing studies with mixed methods. Recent systematic reviews on outcome measurement of breathlessness and a consensus statement, both of which call for unidimensional, multidimensional, and qualitative assessment of the symptom, reflect this stance.[64–67]

Design Issues

1. Clarification of the primary endpoint has been a key factor. Understanding that our main attention should lie with the sensation of breathlessness has resulted in adequately powered studies.[9,51] An appreciation of the subtleties of measurement of the sensation of breathlessness also has been important; there appears to be a diurnal variation in the perception of intensity, so assessment of "present" breathlessness in daily measurement needs to be measured twice daily (e.g., on awakening and before going to bed).[18] We also have improved our understanding in how best to use unidimensional measures such as the NRS, the Borg scale, and the VAS, choosing with much more care which tool to use for which population, and in what situation.[64–67] Measurement of function is still an important but secondary endpoint.
2. Attrition in palliative care studies unrelated to the intervention is a predictable issue. Methods for accounting for dropouts unrelated to the intervention and missing data should be planned for in sample size calculation (some studies will experience at least a 40% dropout rate by four weeks, which should be planned into the sample size),[61] study design, and statistical analysis plans, especially for those involving longitudinal analyses.
3. Meticulous adverse event monitoring is mandatory. There is a tendency in palliative care to make the assumption that it is not possible to make matters any worse by "trying something out."[16] This is an erroneous assumption, and any clinical trial should come under the same scrutiny with regard to adverse events as any other.[16]
4. The sensation of breathlessness is driven by many factors; therefore, randomization is needed to minimize such bias in efficacy studies.
5. Large pharmacovigilance studies and well-designed, observational, consecutive cohorts within which we have meaningful prospectively collected data to draw stratified conclusions are invaluable for assessing many of the questions posed earlier. For example, subgroups hypothesized to be most likely to respond can be assessed using multivariate analyses and the multiple inputs for the "dyspnea target" could be addressed. Sufficient recruitment to such cohort studies requires multicenter collaboration.
6. Well-designed qualitative studies to understand clinical decision making, barriers, and facilitators regarding the use of opioids for breathlessness, and user experience are needed to help inform education and dissemination of research findings, as knowledge of the evidence base alone is insufficient to lead to change in practice.[68]

Study Infrastructure

1. Recruitment methods remain an ongoing challenge, but methods outlined by Abernethy et al.[18,60] have proved their worth in successful, multinational interventional studies in palliative care populations.
2. The establishment of collaborative relationships can access pooled resources, and provide an important way forward.[13,14] Six ongoing rigorous Phase III drug trials in

several Australian palliative care centers are recruiting well, demonstrating that well-funded, well-structured collaborative studies can be completed, even in frail palliative care populations, if clinical centers are given the research infrastructure resources to contribute to large projects. A main key to success is to keep the project as simple and achievable as possible, with a reduction in extraneous variables.[69]

Research Questions

1. The MCID in chronic breathlessness calculated from subjective patient data is important, and should be one of the first aspects of the research agenda to give patient-related relevance to research outputs.
2. There is a need to define what is meant by "episodic breathlessness related and unrelated to exertion," as this appears to be a particularly challenging clinical situation and clear definitions are needed as a first step to study design.
3. Rapid-onset opioids are an attractive therapeutic option especially for acute crises, although careful delivery will be required, especially in the opioid-naïve person.
4. Synergism with other approaches such as opioids with or without oxygen, benzodiazepines, selective serotonin reuptake inhibitors, and related drugs should be explored. Similarly, opioids in conjunction with the vast array of nonpharmacological approaches is an area ripe for exploration, especially using the "total dyspnea" model.
5. We have barely scratched the surface of understanding how opioids work in helping the sensation of breathlessness. One of the barriers to further exploration using fMRI is that people with breathlessness as a result of advanced illness find it difficult to tolerate magnetic resonance imaging scanning. Novel methods are being explored to address this issue.

Conclusions

We have achieved much in our understanding of the use of opioids for the relief of chronic breathlessness. Strands are coming together from work done including expanding science in neuroimaging, pain, heart failure, COPD, and cancer. However, there is a clear warning to heed; to move forwards to answer remaining questions, we need to work together in collaborative groups. Those groups need to be big enough to recruit sufficient numbers of study participants and should include people with a range of skills including physiologists, neuroimagers, trial methodologists, and qualitative researchers. Let us put our energy, and the energy of the patients who want to help us, into studies that will truly further our understanding in this important area.

Disclosures and Acknowledgments

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The authors declare that they have no financial or personal relationships with individuals, organizations, or companies that might be perceived to bias the work.

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