The Role of Inhaled Opioids and Furosemide for the Treatment of Dyspnea

Richard H Kallet MSc RRT FAARC

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Summary

Numerous case reports, uncontrolled studies, and small randomized placebo-controlled trials have investigated the role of aerosolized opioids in the treatment of both dyspnea and pain. Recently, aerosolized furosemide was studied for the treatment of dyspnea. A direct effect on either pulmonary stretch receptors or irritant receptors has been proposed to explain the apparent effectiveness of these drugs. A review of the literature found 37 studies and reports: 23 on aerosolized opioids to treat dyspnea, 7 for analgesia, and 7 on aerosolized furosemide. In general, prospective double-blind randomized placebo-controlled trials have investigated the effects of aerosolized opioids on dyspnea and exercise tolerance in patients with stable chronic cardiopulmonary disease, and found no effect. In contrast, the vast majority of studies found that aerosolized opioids relieved dyspnea better than parenteral opioids and with less systemic adverse effects in patients with terminal lung cancer and cystic fibrosis. However, most of these findings come from uncontrolled studies and case reports. Aerosolized opioids also have been found to provide effective analgesia, again with less systemic adverse effect. Small, generally uncontrolled, studies suggest that aerosolized furosemide may relieve dyspnea both in patients with terminal cancer and those with chronic obstructive pulmonary disease. Routine clinical use of aerosolized opioids to treat dyspnea in terminal illness will require large randomized placebo-controlled trials. However, until these studies are done, the risk/benefit ratio favors use of aerosolized opioids and furosemide in selected patients, based on the principle of compassionate care. Key words: dyspnea, breathlessness, aerosolized morphine, aerosolized furosemide, palliative care, chronic obstructive pulmonary disease. [Respir Care 2007;52(7):900–910. © 2007 Daedalus Enterprises]
Introduction

Dyspnea is commonly encountered in patients with a variety of terminal diseases, such as metastatic cancer, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, congestive heart failure, and several neurological conditions. Between 33% and 47% of the general cancer population experience dyspnea,\textsuperscript{1,2} and the incidence increases to 55–70% for those in the terminal stage.\textsuperscript{3,4} In over 20% of these patients, dyspnea is reported to be the primary symptom.\textsuperscript{5} In contrast to pain, which tends to be well-controlled in the final weeks of life, dyspnea progressively increases in frequency and intensity, particularly in those with primary lung cancer.\textsuperscript{6} As breathing is the primal sensation of life, its disturbance evokes the most profound sense of dread. And in those grappling with terminal illness, dyspnea provokes psychological suffering, as it is invariably associated with impending death.

Often, reversing the underlying cause of dyspnea in the terminally ill is not feasible, so palliation of the symptom becomes the primary goal. Opioids have been used to treat dyspnea since the late 19th century, but their use fell from favor in the 1950s, once a clear relationship with respiratory depression was established.\textsuperscript{7} In the 1980s, peripheral opioid receptors were discovered throughout the body,\textsuperscript{8} thus raising the possibility that a direct pulmonary-targeted treatment for dyspnea with aerosolized opioids might be possible with less adverse effect.

This paper will review the scientific literature on the use of inhaled opioids for the treatment of dyspnea. This will be preceded by a brief review of the theoretical mechanisms of dyspnea, the pharmacology of opioids, and the causes of dyspnea in terminal illness. The paper will conclude with a description of new research that suggests aerosolized furosemide may be an effective alternative for the treatment of dyspnea.

Psychophysical Dimensions of Dyspnea

The perception of difficult breathing is a complex phenomenon, possessing diverse qualities best illustrated by the distinction between 2 words that are often used interchangeably: dyspnea and breathlessness. Whereas dyspnea refers to excessive exertion during the act of breathing, breathlessness is the unpleasant urge to breathe that is closely associated with suffocation and breath-holding.\textsuperscript{9} For simplicity, the term dyspnea will be retained in this paper.

Contemporary theories posit that dyspnea emanates from multiple sensory inputs that are integrated in the brain, which then evoke a response, both in terms of efferent discharge to the breathing muscles and to the sensory cortex (corollary discharge).\textsuperscript{10} A shared characteristic between dyspnea and pain is the existence of a diverse vocabulary expressing sensational nuances related to underlying pathophysiologic derangements.\textsuperscript{11} Moreover, dyspnea involves not only the generation of an unpleasant sensation, but a subjective response to it.\textsuperscript{12} As with all perception, dyspnea is interpreted within the context of previous experience and learning, so that an individual’s reaction to dyspnea frequently changes over time.\textsuperscript{13} Therefore, the intensity of distress that accompanies dyspnea is highly individualized, and objective measures of lung function often bear little resemblance to how patients assess their quality of breathing.\textsuperscript{12} It is important to emphasize that efferent discharge from the respiratory centers in the brain stem represents a complex processing and integration of multiple inputs, which include: afferent information regarding peripheral chemoreceptor stimulation; force-displacement in the chest wall; lung stretch; central chemoreceptor stimulation; and information from higher levels in the brain (Fig. 1).

A useful concept for understanding dyspnea is length-tension inappropriateness\textsuperscript{14} or neuromechanical dissociation.\textsuperscript{15} When efferent signals to the respiratory muscles cause contraction, mechanoreceptors in muscle fibers, ten-
dons and joints, and also in the airways and alveoli, evoke afferent information that conveys both the velocity and degree of displacement occurring in the chest wall and lungs. In this way, effort (efferent discharge from the respiratory centers in the brain stem), force developed in the inspiratory muscles, velocity, and displacement of the lungs and chest wall are integrated. Through habituation we come to experience a specific relationship between these elements as “normal breathing.” Minor breath-to-breath imbalances that develop between force and displacement are used as a servo-mechanism, processed either at the spinal or medullary level, to adjust breathing effort and maintain minute ventilation. However, when tension in the ventilatory muscles is excessive, relative to both the shortening of the muscle fibers and the stretch of the lung tissue, dyspnea is evoked, as heightened efferent discharge to the respiratory muscles also causes stimulation of the reticular system, which evokes conscious awareness. Likewise, dyspnea can occur in the presence of muscle weakness or fatigue, when length-tension appropriateness may be preserved but effort is disproportional to chest displacement. Of particular interest is the fact that breathlessness can be evoked independently of other stimuli, by elevated carbon dioxide.

Furthermore, the context in which these signals occur impacts the interpretation of breathing sensations. For example, during heavy exercise the corresponding respiratory effort and work load are elevated, but this does not provoke distress because it is appropriate to the circumstances, and respiratory effort can be reduced simply by decreasing the activity level. However, if the same breathing pattern were to occur when sitting quietly in bed, it would elicit alarm, as the breathing pattern is inappropriate. More importantly, it implies that the subject cannot do anything to rectify the abnormality.

Etiology of Dyspnea in Terminal Illness

Because multiple physiologic inputs are responsible for generating dyspnea, numerous pathophysiologic disturbances can impact the intensity and quality of the sensation. When examining factors that contribute to dyspnea in advanced diseases, it is apparent that some factors can be treated readily, whereas others are not amenable to rapid reversal (Table 1). Thus, treatment should focus initially on salient causes of dyspnea, such as correction of hypoxemia with supplemental oxygen, acute hypercapnia with noninvasive positive-pressure ventilation, reversal of bronchospasm with β agonist and steroids, relief of chest wall restriction by drainage of pleural effusions or ascites, and reduction of pulmonary edema with diuretics. Palliative therapy with aerosolized opioids should be considered only when conventional approaches do not produce satisfactory results or corrective treatment is not plausible. In particular, muscle weakness, anxiety, and panic appear to be common features of advanced disease that greatly impact dyspnea but may not be amenable to standard therapies, and thus may form a strong rationale for using aerosolized opioids.

Pharmacology

In the 1970s it was discovered that the central nervous system produces endogenous opioids (endorphins) that are important in regulating not only the perception of pain, but also sleep, learning, memory, and appetite. In particular, endorphins are up-regulated in response to both stress and chronic pain. In brief, endorphins modulate afferent impulses, so that the perception of pain (nociception) is either altered or inhibited. That the medulla was discovered to be rich in opiate receptors provided the first anatomic evidence for the long-recognized effects of exogenous opiates on respiratory drive.

Although they do not play a regulatory role in the control of breathing in normal subjects, endorphins blunt the ability of patients with COPD to compensate for increased resistive work load (but not carbon dioxide sensitivity). Similar to the body’s response to chronic pain, the brain up-regulates endorphins as an adaptive response to the chronic stress associated with increased work of breathing. A similar effect is achieved with oral dihydrocodeine, which improves mobility and dyspnea in ambulatory patients with COPD, and with subcutaneous morphine sulfate to ameliorate dyspnea in patients with terminal cancer.

By the early 1980s, opioid receptors were discovered on peripheral sensory nerves throughout the body. These receptors, which are found at multiple locations, are up-regulated during inflammation, as a result of interactions with the immune system. In brief, opioids decrease calcium currents within the cell bodies, which inhibits neuronal firing and transmitter release. In addition, opioids depress the release of pro-inflammatory “Substance P,” which may help to decrease local inflammation. It is postulated that during inflammation the normally impermeable perineurium sheath that protects nerve fibers is disrupted, allowing access to opioid agonists and possibly the activation and peripheral migration of opioid receptors within the nerve.

Three main opioid receptors have been identified in the respiratory tract: μ (MOR), δ (DOR), and κ (KOR), which mediate the effects of the 3 primary families of endogenous opioids (endorphins, enkephalins, and dynorphins, respectively) as well as exogenous opioids such as morphine and codeine. In addition, the lungs also may contain a novel opioid receptor. Animal studies have revealed the presence of opioid receptors in the trachea, bronchi, and pulmonary arteries, but these receptors are...
particularly prominent in the bronchioles and the alveolar walls near the pulmonary capillaries.\textsuperscript{26}

Pulmonary opioid receptors are associated primarily with vagal afferent C-fibers (irritant or rapidly-adapting fibers) and the juxta-pulmonary capillary receptors (J-receptors), which are located in the alveolar wall.\textsuperscript{27} Stimulation of C-fibers in the small airways and J-receptors in the alveoli by acute pulmonary congestion and edema, multiple pulmonary embolisms, and inflammation may be responsible, in part, for triggering the sensation of dyspnea, as well as tachypnea, bronchoconstriction, and increased airway secretions.\textsuperscript{27,28} In a manner analogous to pain, opioids may alter the perception of dyspnea by modifying signals from pulmonary afferent C-fibers. A third type of vagal afferent fiber is the pulmonary stretch receptors that, when stimulated, typically by large tidal volumes, reduce the sensation of air hunger. Inhaled opioids also may act on these fibers.

**Pharmacokinetics**

Despite the anatomic evidence cited above, it remains unclear whether the effects of aerosolized opioids on dyspnea are due to modifications in peripheral afferent signaling that alters proprioception, or that opioids absorbed into the systemic circulation act on central nervous system control of breathing. Most studies that have examined inhaled opioids did not observe signs of sedation or respiratory depression.\textsuperscript{29–34} However, hypercapnia\textsuperscript{35} and profound respiratory depression\textsuperscript{36} occasionally have been

### Table 1. Pathophysiology of Dyspnea in Terminal Illness

<table>
<thead>
<tr>
<th>Disease State</th>
<th>Physiologic Factors</th>
<th>Mechanisms That Contribute to Dyspnea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>Muscle weakness: ↓ muscle bulk, deconditioning, ↓ perfusion ↓ lung compliance: engorgement/pulmonary edema. ↓ chest wall compliance: ascites Diffusion defect: hypoxemia ↑ airways resistance and bronchial sensitivity ↑ Vd/Vt, ↓ Vt and ↓ lung perfusion → hypercapnia</td>
<td>Imbalance: effort vs displacement Imbalance: force vs displacement ↑ respiratory drive Imbalance: force vs displacement ↑ respiratory drive ↑ respiratory drive, ↑ perceptual focus on breathing</td>
</tr>
<tr>
<td>Idiopathic pulmonary fibrosis</td>
<td>↓ lung compliance: lung scarring Diffusion defect: hypoxemia Muscle weakness: ↓ muscle bulk, deconditioning Anxiety, depression, panic</td>
<td>Imbalance: force vs displacement ↑ respiratory drive ↑ respiratory drive, ↑ perceptual focus on breathing</td>
</tr>
<tr>
<td>COPD</td>
<td>Muscle weakness: deconditioning, altered geometry from hyperinflation ↓ lung compliance from hyperinflation ↑ airways resistance ↑ Vd/Vt → hypercapnia ↑ V/Q mismatching → hypoxemia</td>
<td>Imbalance: force vs displacement Imbalance: force vs displacement ↑ respiratory drive ↑ respiratory drive ↑ respiratory drive, ↑ perceptual focus on breathing</td>
</tr>
<tr>
<td>Neurologic diseases</td>
<td>Muscle weakness</td>
<td>Loss of airway control: choking ↑ airways resistance: retained secretions ↓ lung compliance: pneumonia Anxiety, depression, panic</td>
</tr>
</tbody>
</table>

\(V_d/V_t\) = ratio of dead space to tidal volume
COPD = chronic obstructive pulmonary disease
V/Q = ventilation-perfusion
Inhaled opioids also provide effective analgesia, which suggests the possibility that dyspnea is modified, at least in part, through a central mechanism. Systemic absorption of opioids may occur from the pulmonary circulation. But a more likely source is absorption from the gastrointestinal tract, due to aerosol impaction in the oropharynx and subsequent swallowing of opioid-containing secretions. Yet in cancer patients who suffer from intractable dyspnea, relatively small amounts of inhaled opioids appear to improve breathing comfort, despite the fact that these patients already are receiving high levels of parenteral opioids for pain management.

Six studies have assessed absorption and bioavailability of morphine, morphine-6-glucuronide (a potent metabolite of morphine), and fentanyl, administered via jet nebulizer with mask, during spontaneous breathing. Allergic reactions or dyspnea were not reported. In contrast, all the uncontrolled trials studies and case reports on the effects of aerosolized opioids in patients with COPD or idiopathic pulmonary fibrosis, or cystic fibrosis, or in healthy volunteers.6 There also have been 13 (mostly uncontrolled) studies and case reports on the effects of aerosolized opioids in end-stage cardiopulmonary disease (COPD, idiopathic pulmonary fibrosis, and congestive heart failure), advanced cancer,29 –33,36,42,57,58 and in healthy volunteers.56 In an unusual case report, a patient with severely debilitating paroxysmal coughing was successfully treated with aerosolized morphine.

Five of the 6 double-blinded randomized placebo-controlled studies that examined the effects of aerosolized opioids in patients with COPD or idiopathic pulmonary fibrosis reported no improvement either in exercise tolerance or dyspnea, compared to placebo. In the one positive study, the improvement in exercise endurance was minor. In contrast, all the uncontrolled trials and case studies that examined the effects of aerosolized opioids in patients with end-stage disease (usually metastatic cancer) reported subjective improvements in dyspnea, paroxysmal coughing, and breathing pattern following aerosolized opioids. Characteristically, in these studies patients appeared to have intractable dyspnea despite receiving generous amounts of intravenous or oral opioids for pain management. Yet supplementation with 5–10 mg of aerosolized morphine sulfate, repeated either as-necessary or every 4 h, almost uniformly improved dyspnea, breathing pattern, and the general appearance of these patients. In patients with opioid tolerance the dose often needed to be increased to approximately 20 mg, and in the final days of life, doses as high as 45–70 mg sometimes were required.

As morphine sulfate can cause bronchospasm from histamine release, some have added a 2–4-mg dose of dexamethasone as prophylaxis. Others have used an initial test dose of only 2.5 mg morphine sulfate to evaluate any

**Aerosolized Opioids in the Management of Dyspnea**

A PubMed title word search from 1965 through 2006 was done, using various combinations of the terms dyspnea, breathlessness, aerosolized, nebulized, opioids, morphine, fentanyl, and hydromorphone. The references for each found paper also were searched to cull additional publications. A total of 30 studies were found (Table 2). Seven of these were small prospective randomized placebo-controlled trials that examined the effects aerosolized morphine sulfate on exercise endurance in patients with stable COPD or idiopathic pulmonary fibrosis, or in healthy volunteers. There also have been 13 (mostly uncontrolled) studies and case reports on the effects of aerosolized opioids in patients with end-stage cardiopulmonary disease (COPD, idiopathic pulmonary fibrosis, and congestive heart failure), advanced cancer, and idiopathic pulmonary fibrosis, or in healthy volunteers. In an unusual case report, a patient with severely debilitating paroxysmal coughing was successfully treated with aerosolized morphine.
<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Subjects</th>
<th>n</th>
<th>Design</th>
<th>Intervention</th>
<th>Evaluation</th>
<th>Results</th>
<th>Overall Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chrubasik</td>
<td>1987</td>
<td>Postoperative abdominal surgery</td>
<td>20</td>
<td>Randomized</td>
<td>Supplemental morphine sulfate via intravenous or aerosol. Dosing strategy unclear, mean doses not different (23 mg vs 21 mg, respectively)</td>
<td>Vital signs, $P_{CO_2}$, subjective report, adverse effects</td>
<td>No difference in vital signs, $P_{CO_2}$ ↓ adverse effects with aerosolized morphine sulfate</td>
<td>+</td>
</tr>
<tr>
<td>Young</td>
<td>1989</td>
<td>Advanced COPD</td>
<td>11</td>
<td>Double-blinded randomized placebo-controlled crossover</td>
<td>5 mg morphine sulfate</td>
<td>Endurance at 80% maximum workload</td>
<td>Mean increase of 35%</td>
<td>+</td>
</tr>
<tr>
<td>Worsley</td>
<td>1990</td>
<td>Post-surgery</td>
<td>20</td>
<td>Randomized placebo-controlled</td>
<td>100 and 300 $\mu$g fentanyl citrate</td>
<td>Visual analog scale, time to alternative analgesia to treat pain</td>
<td>↓ visual analog scale, ↑ time to alternative analgesia</td>
<td>+</td>
</tr>
<tr>
<td>Higgins</td>
<td>1991</td>
<td>Post-surgery</td>
<td>30</td>
<td>Double-blinded randomized placebo-controlled</td>
<td>64, 159, and 318 $\mu$g fentanyl citrate</td>
<td>Visual analog scale, time to “escape analgesia” to treat pain</td>
<td>↓ visual analog scale at all doses, larger ↓ in visual analog scale and ↑ time to additional analgesia at higher doses.</td>
<td>+</td>
</tr>
<tr>
<td>Farncombe</td>
<td>1993</td>
<td>End-stage COPD, CHF, IPF</td>
<td>4</td>
<td>Uncontrolled</td>
<td>5 mg morphine sulfate every 4 h, ↑ to 18–25 mg</td>
<td>Subjective report</td>
<td>↓ dyspnea, ↑ relaxation</td>
<td>+</td>
</tr>
<tr>
<td>Beauford</td>
<td>1993</td>
<td>Stable COPD</td>
<td>8</td>
<td>Double-blinded randomized placebo-controlled crossover</td>
<td>1, 4, and 10 mg morphine sulfate</td>
<td>Maximum exercise, dyspnea (Modified Borg Scale), $V_{E}$, $V_{O_2}$</td>
<td>No difference</td>
<td>-</td>
</tr>
<tr>
<td>Tooms</td>
<td>1993</td>
<td>End-stage mesothelioma</td>
<td>1</td>
<td>Case report</td>
<td>5 mg morphine sulfate every day</td>
<td>Subjective report</td>
<td>↓ distress</td>
<td>+</td>
</tr>
<tr>
<td>Farncombe</td>
<td>1994</td>
<td>Advanced cancer</td>
<td>3</td>
<td>Uncontrolled</td>
<td>5–15 mg morphine sulfate every 4 h</td>
<td>Subjective report, breathing pattern</td>
<td>↓ dyspnea, ↓ respiratory rate, ↑ relaxation</td>
<td>+</td>
</tr>
<tr>
<td>Masood</td>
<td>1995</td>
<td>Stable COPD</td>
<td>12</td>
<td>Double-blinded randomized placebo-controlled crossover</td>
<td>10 and 25 mg morphine sulfate</td>
<td>Exercise endurance, dyspnea (visual analog scale)</td>
<td>No difference</td>
<td>-</td>
</tr>
<tr>
<td>Harris-Eze</td>
<td>1995</td>
<td>IPF</td>
<td>6</td>
<td>Double-blinded randomized placebo-controlled crossover</td>
<td>2.5 and 5 mg morphine sulfate</td>
<td>Exercise endurance, dyspnea (Modified Borg Scale), $V_{O_2}$, $V_{CO_2}$</td>
<td>No difference</td>
<td>-</td>
</tr>
<tr>
<td>Masood</td>
<td>1995</td>
<td>Healthy males</td>
<td>12</td>
<td>Double-blinded randomized placebo-controlled crossover</td>
<td>10 and 25 mg morphine sulfate, compared to both placebo and intravenous 1 and 2.5 mg</td>
<td>Exercise endurance, dyspnea (visual analog scale)</td>
<td>No difference</td>
<td>-</td>
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<tr>
<td>Leung</td>
<td>1996</td>
<td>Stable COPD</td>
<td>10</td>
<td>Double-blinded randomized placebo-controlled crossover</td>
<td>5 mg morphine sulfate</td>
<td>Exercise endurance, dyspnea (Modified Borg Scale), $V_{E}$</td>
<td>No difference</td>
<td>-</td>
</tr>
<tr>
<td>Noseda</td>
<td>1997</td>
<td>Severe COPD (14 of the 17 patients had severe airflow limitation), CHF, IPF</td>
<td>17</td>
<td>Double-blinded randomized placebo-controlled crossover</td>
<td>10 and 20 mg morphine chlorhydrate, compared to both placebo and oxygen therapy</td>
<td>Dyspnea (visual analog scale)</td>
<td>No difference</td>
<td>-</td>
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<tr>
<td>Jankelson</td>
<td>1997</td>
<td>Stable COPD</td>
<td>16</td>
<td>Double-blinded, randomized placebo-controlled crossover</td>
<td>20 and 40 mg morphine sulfate</td>
<td>6-min walk distance, dyspnea (subjective report)</td>
<td>No difference</td>
<td>-</td>
</tr>
<tr>
<td>First Author Year</td>
<td>Subjects</td>
<td>n</td>
<td>Design</td>
<td>Intervention</td>
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<tr>
<td>Stein 1997</td>
<td>Advanced cancer</td>
<td>1</td>
<td>Case report</td>
<td>2.5 mg morphine sulfate every 4 h ↓ to every day at bedtime</td>
<td>Effect on severe, paroxysmal coughing</td>
<td>Cessation of paroxysmal coughing</td>
<td></td>
<td></td>
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<tr>
<td>Zeppetella 1997</td>
<td>Advanced career</td>
<td>17</td>
<td>Uncontrolled</td>
<td>20 mg morphine sulfate every 4 h over 48 h</td>
<td>Dyspnea (Dyspnea Assessment Questionnaire)</td>
<td>↓ Dyspnea Assessment Questionnaire score at 24 h</td>
<td></td>
<td></td>
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<tr>
<td>Lang 1998</td>
<td>Advanced cancer</td>
<td>1</td>
<td>Case report</td>
<td>4 mg morphine sulfate + 4 mg dexamethasone</td>
<td>Dyspnea</td>
<td>Severe respiratory and cardiovascular depression</td>
<td></td>
<td></td>
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<tr>
<td>Tanaka 1999</td>
<td>Advanced cancer</td>
<td>15</td>
<td>Uncontrolled</td>
<td>20 mg morphine chloride</td>
<td>Dyspnea (visual analog scale)</td>
<td>↓ visual analog scale</td>
<td></td>
<td></td>
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<tr>
<td>Sarhill 2000</td>
<td>Advanced cancer</td>
<td>1</td>
<td>Case report</td>
<td>4 mg hydromorphone every 4 h</td>
<td>Dyspnea (subjective report)</td>
<td>↓ dyspnea and anxiety, ↑ relaxation and exercise tolerance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Janahi 2000</td>
<td>Cystic fibrosis</td>
<td>1</td>
<td>Case report</td>
<td>2 mg morphine sulfate every 4 h + 2 mg dexamethasone</td>
<td>Dyspnea (Modified Borg Scale)</td>
<td>↓ Modified Borg Scale and P&lt;sub&gt;CO₂&lt;/sub&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohen 2002</td>
<td>Cystic fibrosis</td>
<td>1</td>
<td>Case report</td>
<td>2.5–12.5 mg morphine sulfate</td>
<td>Dyspnea (visual analog scale)</td>
<td>↓ visual analog scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graff 2004</td>
<td>Cystic fibrosis</td>
<td>1</td>
<td>Case report</td>
<td>25–50 μg fentanyl citrate every 4 h</td>
<td>Dyspnea (Modified Borg Scale), S&lt;sub&gt;PO₂&lt;/sub&gt;, activity level</td>
<td>↓ dyspnea in 81%, ↓ visual analog scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coyne 2002</td>
<td>Advanced cancer</td>
<td>35</td>
<td>Uncontrolled</td>
<td>25 μg fentanyl citrate</td>
<td>Dyspnea (subjective report)</td>
<td>↓ visual analog scale</td>
<td></td>
<td></td>
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<tr>
<td>Quigley 2002</td>
<td>Advanced cancer</td>
<td>9</td>
<td>Uncontrolled</td>
<td>5, 10, or 20 mg morphine-6-glucuronide</td>
<td>Dyspnea (visual analog scale)</td>
<td>↓ visual analog scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rutherford 2002</td>
<td>Asthma</td>
<td>1</td>
<td>Case report</td>
<td>Morphine sulfate (dose not reported) × 2.5 years</td>
<td>Total disability, severe paroxysmal coughing</td>
<td>Marked ↓ coughing, ↑ quality of life</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bartfield 2003</td>
<td>Abdominal pain in emergency department</td>
<td>50</td>
<td>Double-blinded randomized placebo-controlled</td>
<td>1.5 μg/kg fentanyl citrate vs intravenous fentanyl citrate</td>
<td>Pain (visual analog scale)</td>
<td>Decrease in visual analog scale not different at 30 min for intravenous vs inhaled</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balts 2004</td>
<td>Acute sickle-cell crisis</td>
<td>2</td>
<td>Case report</td>
<td>20 mg morphine sulfate every 6 h</td>
<td>Chest-wall pain (verbal report on a 1–10 scale)</td>
<td>Pain ↓ 50–90%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bruera 2005</td>
<td>Advanced cancer</td>
<td>11</td>
<td>Double-blind randomized placebo-controlled crossover</td>
<td>Aerosolized morphine sulfate vs subcutaneous 45 mg morphine sulfate</td>
<td>Dyspnea Intensity Score</td>
<td>↓ Dyspnea Intensity Score, compared to placebo. No efficacy difference between inhaled and subcutaneous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fulda 2005</td>
<td>Post-traumatic chest injury</td>
<td>44</td>
<td>Double-blinded randomized placebo-controlled</td>
<td>Aerosolized morphine sulfate vs patient-controlled analgesia via intravenous pump; 12 mg aerosolized 6.2 mg patient-controlled every 4 h</td>
<td>Chest-wall pain (visual analog scale), Sedation Score</td>
<td>↓ visual analog scale, compared to placebo. No efficacy difference between inhaled and patient-controlled. ↓ sedation with inhaled</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lefèvre 2006</td>
<td>Musculoskeletal pain in emergency department</td>
<td>102</td>
<td>Uncontrolled</td>
<td>Morphine sulfate: 0.2 mg/kg Fentanyl citrate: 3 μg/kg Alfentanil: 15 μg/kg</td>
<td>Pain (verbal report on a 1–10 scale)</td>
<td>Approximately 50% ↓ in pain</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

COPD = chronic obstructive pulmonary disease  
CHF = congestive heart failure  
IPF = idiopathic pulmonary fibrosis  
S<sub>PO₂</sub> = oxygen saturation measured via pulse oximetry  
V<sub>CO₂</sub> = carbon dioxide production  
V<sub>E</sub> = minute ventilation  
V<sub>O₂</sub> = oxygen consumption. V<sub>θ</sub>/V<sub>T</sub> = ratio of dead space to tidal volume.
tendency for bronchospasm prior to administering a higher dose.\textsuperscript{7} Fentanyl does not cause histamine release and therefore is an attractive alternative in severely dyspneic patients with reactive airways disease. Doses of 20–100 \(\mu g\) of fentanyl have been used to treat dyspnea.\textsuperscript{7,31,60} With hydromorphone an initial aerosolized dose of 1–2 mg every 4 h has been recommended,\textsuperscript{7} but doses as high as 4–8 mg every 4 h have been used.\textsuperscript{4,58,63}

Only 2 prospective, randomized, double-blinded, placebo-controlled trials have examined the efficacy of aerosolized opioids on dyspnea in patients with advanced disease. Noseda et al\textsuperscript{32} found no benefit from 10 mg or 20 mg of aerosolized morphine citrate on dyspnea in 17 patients with severe chronic lung disease or metastatic cancer. In contrast, Bruera et al\textsuperscript{33} found that aerosolized morphine sulfate given to patients with metastatic cancer was as effective as subcutaneous administration in reducing dyspnea. These discrepant results may be explained by the fact that 12 of the 17 patients in the study by Noseda et al\textsuperscript{32} had COPD, whereas only 3 had metastatic cancer. Two of the patients with cancer died before completing the protocol, and their data were not included in the analysis. In addition, Noseda et al\textsuperscript{32} measured dyspnea only 10 min after completion of nebulization, which based on the results of aerosolized opioid studies for pain management,\textsuperscript{34,38,41} may have been an insufficient amount of time to accurately judge efficacy.

**Aerosolized Opioids in the Management of Pain**

Seven studies have evaluated aerosolized opioids for analgesia in postoperative management following general surgery,\textsuperscript{38–40} chest trauma,\textsuperscript{34} sickle cell crisis,\textsuperscript{62} and management of pain in the emergency department setting.\textsuperscript{37,41} All the studies found that aerosolized opioids provide adequate analgesia, and several reported a lower incidence of adverse effects, including sedation.\textsuperscript{34,37,38} Average doses that provide adequate analgesia appear to be 12–20 mg morphine sulfate every 4–6 h,\textsuperscript{34,38,62} and 150–300 \(\mu g\) fentanyl citrate.\textsuperscript{37,40,41} Only one of the studies with fentanyl allowed repeated supplemental administration, which was at half the initial dose.\textsuperscript{37}

When compared to intravenous administration, aerosolized opioids tend to have a slower onset of action, but the quality of analgesia is not different by 30 min.\textsuperscript{34,38,41} Some studies reported onset of pain relief in 3–5 min.\textsuperscript{37,40,62} Although routinely administering aerosolized opioids for analgesia has been criticized as awkward and inefficient,\textsuperscript{40} it may be useful as a temporizing measure in patients in whom either intravenous access is difficult or the adverse effects of sedation must be avoided.

**Occupational Exposure Risks to Health Care Providers**

Health care professionals have a propensity for developing chemical dependencies.\textsuperscript{64} Anesthesiologists appear to be at particular risk, and this has been attributed to a combination of high job stress and extraordinary access to controlled substances.\textsuperscript{65} Yet others postulate that inadvertent aerosolization of intravenously administered opiates in the exhaled gas may sensitize health care workers through “second-hand” exposure.\textsuperscript{64} Over time this sensitization may enhance the probability of addiction.

Aerosolized fentanyl and propofol have been detected in the operating theater and in the expiratory limb of anesthesia ventilator circuits.\textsuperscript{66} This raises concern regarding occupational risk. However, the potential for aerosolized opioid exposure is much greater in the critical care environment, given the tremendous frequency of intravenous infusions of high-dose opioids and the elevated minute ventilation demands of patients. Yet there is no evidence of widespread opiate addiction among critical care practitioners, which suggests that access to these drugs without stringent accountability is a more likely explanation. At this juncture, theoretical concerns over health care worker exposure should not preclude consideration of aerosolized opioid therapy in patients with terminal illness. Nevertheless, future prospective studies of aerosolized opioid therapy should evaluate environmental pollution to assess potential risks to health care providers.

**Aerosolized Furosemide in the Treatment of Dyspnea**

The potential effectiveness of aerosolized furosemide to treat dyspnea was first reported in a patient with end-stage Kaposi’s sarcoma.\textsuperscript{67} Recent uncontrolled studies\textsuperscript{68,69} examined the potential of aerosolized furosemide to reduce dyspnea in patients with terminal cancer. Shimoyama and Shimoyama\textsuperscript{68} reported 3 patients with dyspnea that was refractory to treatment, including parenteral morphine sulfate. Aerosolized delivery of 20 mg furosemide reduced dyspnea and respiratory rate, with the onset of effect occurring within 20–30 min and lasting for more than 4 h. In some patients, both respiratory rate and use of accessory muscles also diminished. In each case, diuresis could not explain the improvement in dyspnea, as urine output did not increase during the study period.

Kohara et al\textsuperscript{69} reported that dyspnea was significantly reduced in 12 of 15 patients who received 20 mg of aerosolized furosemide. No change was observed in arterial blood gases, respiratory rate, or heart rate. However, a small double-blinded randomized placebo-controlled study\textsuperscript{70} with 7 patients with advanced cancer found that dyspnea tended to worsen after aerosolized furosemide, but the difference was not significant.
Aerosolized furosemide prevents bronchospasm\textsuperscript{71,72} and may ameliorate dyspnea because of its bronchodilatory effects.\textsuperscript{73–75} Moreover, in experimental models of dyspnea induced by breath-holding,\textsuperscript{76} resistive-loading with and without hypercapnia,\textsuperscript{76} and hypercapnia with constrained ventilation,\textsuperscript{77} 40 mg of aerosolized furosemide increased breath-holding time and reduced dyspnea.

In theory, aerosolized furosemide may reduce dyspnea by suppressing cough and prevents bronchospasm when the lungs are exposed to aerosolized low-chloride solutions.\textsuperscript{78} This suggests that ionic changes in the cellular environment are circumvented, which prevents stimulation of irritant receptors.

On the other hand, dyspnea can be relieved by deep lung inflation through the stimulation of pulmonary stretch receptors.\textsuperscript{79} Furosemide also stimulates pulmonary stretch receptors\textsuperscript{80} and may relieve dyspnea by mimicking the effects of large tidal volumes.\textsuperscript{77} Aerosolized furosemide is believed to stimulate pulmonary stretch receptors by inhibiting cellular ionic transport mechanisms and thus increasing local sodium concentrations.\textsuperscript{76} Although most studies have not observed renal effects from aerosolized furosemide,\textsuperscript{68,76} Moosavi et al\textsuperscript{77} reported brisk diuresis among normal study subjects. Therefore, another potential effect of inhaled furosemide on dyspnea in patients with cardiopulmonary disease may emanate simply from a reduction in pulmonary edema that decreases either respiratory effort or J-receptor stimulation.

Reported adverse effects from aerosolized furosemide were generally mild and included transient nausea, and sleeplessness in some patients.\textsuperscript{69} Among normal research subjects the most frequent adverse effects were pharyngeal and substernal irritation, intermittent cough, and a strong urge to urinate.\textsuperscript{77}

**Summary**

In conclusion, higher-level clinical evidence consistently shows that aerosolized opioids are not effective in improving dyspnea or exercise tolerance in patients with chronic cardiopulmonary diseases, including COPD and idiopathic pulmonary fibrosis. Predominantly low-level clinical evidence supports aerosolized opioids for palliation of dyspnea in patients with advanced cancer and cystic fibrosis. There is some higher level clinical evidence that aerosolized opioids can be utilized for systemic analgesia. However, this should be restricted to circumstances where effective parenteral administration is delayed because of difficulty in achieving intravenous access. Alternatively, lower-level clinical evidence suggests that aerosolized furosemide may reduce dyspnea both in patients with advanced cancer and in those with COPD.

**REFERENCES**