

# An approach to dyspnea in advanced disease

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## ABSTRACT

**INTRODUCTION** To describe an approach to assessment and treatment of dyspnea.

**SOURCES OF INFORMATION** New level I evidence can guide management of dyspnea in advanced illness. Assessment and use of adjuvant medications and oxygen relies on level II and III evidence.

**MAIN MESSAGE** Opioids are first-line therapy for managing dyspnea in advanced illness. They are safe and effective in reducing shortness of breath. Neuroleptics are useful adjuvant medications. Evidence does not support use of oxygen for every patient experiencing dyspnea; it should be tried for patients who do not benefit from first-line medications and nonmedicinal therapies.

**CONCLUSION** Opioids relieve dyspnea and are indicated as first-line treatment for dyspnea arising from advanced disease of any cause.

## RÉSUMÉ

**INTRODUCTION** Proposer une démarche pour l'évaluation et le traitement de la dyspnée.

**SOURCES D'INFORMATION** Il existe de nouvelles preuves de niveau I pour orienter le traitement de la dyspnée observée à un stade avancé de certaines maladies. L'évaluation de la dyspnée et l'utilisation des médicaments adjuvants reposent sur des preuves de niveaux II et III.

**PRINCIPAL MESSAGE** Les opiacés sont des médicaments de premier recours pour soulager la dyspnée dans les maladies terminales. Ils réduisent l'essoufflement de façon sûre et efficace. Les neuroleptiques sont également utiles comme médicaments adjuvants. L'utilisation de l'oxygène chez tous les patients souffrant de dyspnée n'est pas supportée par les données actuelles; un essai avec l'oxygène est toutefois indiqué chez ceux qui n'obtiennent pas d'amélioration avec la médication de premier recours ou les traitements non médicinaux.

**CONCLUSION** Les opiacés réduisent la dyspnée et ils doivent être utilisés en premier recours dans la dyspnée observée au stade avancé de diverses maladies.

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**CME**

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**An approach to dyspnea in advanced disease**

Mr Charles, a 78-year-old man, is admitted with dyspnea secondary to advanced congestive heart failure. This is his fourth admission in as many months. He has a 50-year history of smoking a pack of cigarettes a day and is known to have severe chronic obstructive lung disease (COPD) and heart disease. He is dyspneic at rest; his oxygen saturation is 82% in room air. Pulmonary edema and chronic bronchitis are confirmed on chest x-ray examination. Following admission, he is treated with diuretics, oxygen, and steroids, but he continues to weaken. Discussions with Mr Charles and his family result in a do not resuscitate order and a decision not to admit him to the intensive care unit.

His dyspnea is ongoing despite maximal cardiac and pulmonary therapy, and he spends much of his day hunched over his bedside table. The nurses have been using a visual analogue scale to measure his shortness of breath. He scores 6-7/10 most of the day; the desired comfort level is 2-3/10. His family is extremely concerned because he eats little, is fatigued, and cannot finish a sentence without pausing for breath. He has at times become so dyspneic that he has scored 10/10 on the dyspnea scale and panicked, later telling his nurses he wants to die. They have tried increasing his oxygen and giving him nebulized bronchodilators, but it has taken many minutes for the severe dyspnea to ease, and it has been extremely distressing for Mr Charles and the staff. The staff are asking you to do something to relieve this man's suffering.

**D**yspnea is defined as uncomfortable breathing. This definition does not give clinicians a sense of the suffering associated with this symptom in advanced illness.

The Symptom Burden of Seriously Ill Hospitalized Patients study<sup>1</sup> researchers interviewed 9105 hospitalized adults with advanced disease and collected information on their symptoms, the severity of the symptoms, and the burden of suffering from the symptoms. Dyspnea, pain, anxiety, and depression caused the highest symptom burden on patients. Patients rated dyspnea as difficult to bear as pain. Chochinov et al<sup>2</sup> looked at the relationship between advanced cancer patients' will to live and dyspnea and found that, in the final days of life, will to live

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was directly related to the severity of dyspnea. Many patients would rather die than suffer with dyspnea.

Most publications on dyspnea in advanced illness have focused on lung cancer-induced dyspnea, but many patients with lung cancer also have advanced lung and heart disease (Table 1<sup>3</sup>).<sup>4</sup> It is probably most helpful clinically to view dyspnea in advanced illness as a single entity, regardless of the original cause. With this perspective, dyspnea becomes a "disease," something we as physicians are more used to recognizing. These patients have disabling dyspnea despite maximal conventional therapy for cardiorespiratory disease or cancer. They are likely to be in the last few weeks of their lives, suffering multiple symptoms from organ failure, and having very poor quality of life.<sup>1</sup>

**Table 1. Objective criteria for end-stage pulmonary and cardiac disease**

**PULMONARY DISEASE**

- Disabling dyspnea at rest (forced expiratory volume in 1 s [FEV<sub>1</sub>] <30% predicted)
- Increasingly frequent hospitalizations for chronic obstructive lung disease or infection
- Hypoxemia: oxygen level <55 in room air
- Hypercapnia: carbon dioxide level >50
- Cor pulmonale and right heart failure secondary to pulmonary disease
- Progressive weight loss >10% of total weight over last 6 mo
- Resting tachycardia >100/min

**CARDIAC DISEASE**

- New York Heart Association Stage IV signs of congestive heart failure at rest
- Already optimally treated with recommended cardiac medications
- Ejection fraction of ≤20% on echocardiography
- Symptomatic ventricular and supraventricular arrhythmias
- History of cardiac arrest
- Embolic cardiovascular accident

Information from National Hospice and Palliative Care Organization.<sup>3</sup>

**Sources of information**

The clinical approach to dyspnea is based on expert opinion (level III evidence); assessment includes using validated symptom assessment scales (level II evidence). Management of dyspnea has level I evidence for use of opioids and some complementary therapies, level II evidence for use of oxygen and neuroleptics, and level III evidence for use of benzodiazepines. (Sidebar shows levels of evidence.)

**Levels of evidence**

- Level I At least one properly conducted randomized controlled trial, systematic review, or meta-analysis
- Level II Other comparison trials: nonrandomized, cohort, case-control, or epidemiologic studies, with preferably more than one study
- Level III Expert opinion or consensus statements

**Assessment of dyspnea**

Dyspnea is a subjective symptom similar to pain, so patients are the only ones who know whether they are short of breath or not. Patients with advanced disease could be dyspneic even though their respiratory rates are not elevated. Because it is so common in advanced disease, every patient should be asked about dyspnea. Severity, pattern, triggering factors, associated symptoms, and effect on activities of daily life must be known to make a proper assessment. Patients' psychological state is also important. Those with advanced disease might be very fearful of dying gasping for breath or of any action or event that triggers severe dyspnea, such as coughing or choking.

A visual analogue scale for dyspnea, where 0 is no shortness of breath and 10 is the worst dyspnea ever, can be used to measure severity and assess the effectiveness of therapy. Several scales have been developed specifically for dyspnea in advanced disease.<sup>5</sup> Assessing other related symptoms, such as pain, cough, and anxiety, might be helpful.<sup>6</sup>

No investigations are helpful for measuring dyspnea in advanced disease. Many clinicians make the mistake of equating dyspnea with hypoxia, but the correlation between patients' reports of dyspnea and abnormalities in pulmonary function is very poor.<sup>7</sup> This mistake can result in patients spending their last days of life in a "Star Wars" mask in order to maintain their oxygen saturation above 90%. Patients can still be dyspneic, and they also have difficulty communicating and being close to their loved ones. In terminal illness, it is preferable to be guided by patients' reports of dyspnea and not to measure oxygen saturation unless patients show clinical signs of hypoxia (eg, confusion).

The appropriateness of investigations, such as chest x-ray examinations, blood gas tests, or interventions such as thoracentesis, depends on the stage of disease and patients' goals. In most cases, the burden

of these procedures is great, and they do little to alter management.

**Management**

The goal of management is to control symptoms and maximize quality of life without prolonging or hastening death. The following treatment recommendations presume that patients have advanced illness and severe dyspnea despite appropriate interventions, such as steroids and antibiotics, pleurodesis, transfusions, radiotherapy, chemotherapy, or maximal cardiac and pulmonary medications.

Explaining the cause of dyspnea and the treatment plan to both patients and their families is essential. Reassurance and having a plan for managing severe dyspnea can lessen fear of dying in great distress. If patients are able to go home, a plan for managing an acute exacerbation of dyspnea at home can prevent return trips to the emergency department.

Some general strategies for reducing dyspnea are avoiding exacerbating activities and conserving energy by rearranging the household and activities of daily living. Keeping the room cool and moist and having a fan blowing gently on the patient can be very helpful. The cool air blowing on the face likely triggers reflexes in the trigeminal nerve (level II evidence).<sup>8</sup> Avoid irritants, such as smoke, and keep the number of people in the room to a minimum. When a patient has an acute attack of dyspnea, the most helpful immediate response is to have someone stay with him or her to avoid the panic of being alone.

**Oxygen not always necessary.** It has been a reflex action to give oxygen to patients who are dyspneic, but it is not supported by evidence. One small, double-blind, randomized trial of hypoxic cancer patients<sup>9</sup> showed benefit from oxygen (level II evidence), and a single-blind larger study in a similar population<sup>10</sup> showed that both oxygen and compressed air relieved patients' feeling of dyspnea (level II evidence).

Another study has shown oxygen to benefit hypoxic COPD patients<sup>11</sup> (level II evidence), but not all patients with advanced disease are hypoxic, and little evidence supports giving oxygen to those without hypoxia. Oxygen is costly and cumbersome in the home, so it is preferable if patients can be managed without it. It is reasonable to try an "N of 1" trial of compressed air versus oxygen with patient blinded to what is being given. If patients cannot perceive any improvement of dyspnea with oxygen, it should not be prescribed. Patients should rate dyspnea (both at rest and with activity) on a visual analogue scale.

**Pharmacologic therapy.** Pharmacologic management of dyspnea has been hampered by lack of training in clinical use of opioids and persistent myths about opioids' effects in respiratory disease. Many clinicians avoid opioids except in the last day or so of life because they are concerned about the rise in carbon dioxide levels and respiratory depression in patients with advanced lung disease. This stems from reports of respiratory depression following parenteral administration of opioids such as morphine,<sup>12,13</sup> but the patients in these studies had normal respiratory function. Studies of patients with severe COPD and other chronic lung diseases have not shown any substantial respiratory depression,<sup>14,15</sup> suggesting that dyspnea counteracts any respiratory depression from opioids. There is also no evidence that opioids shorten life.<sup>16</sup> While administration of opioids might raise carbon dioxide levels slightly, the concentration is not related to prognosis in patients with chronic lung disease treated with long-term oxygen therapy.<sup>17</sup>

Some small crossover studies have shown the benefit of opioids for dyspnea,<sup>18,19</sup> and a systematic review (level I evidence) of use of oral and parenteral opioids in advanced illness has shown substantial benefit in reducing the feeling of breathlessness in patients with advanced disease of any cause.<sup>20</sup> The same review did not show benefit from nebulized opioids (level I evidence). Recently, a randomized placebo-controlled, crossover trial showed morphine was of substantial benefit in managing dyspnea in advanced disease due to COPD, cancer, and other respiratory illnesses.<sup>21</sup>

It is important to distinguish between patients who have not been taking opioids regularly for at least several days and patients who are already taking opioids regularly for pain or dyspnea. In those already taking opioids, the baseline dose can be increased by 25% to 50% depending on the severity of dyspnea. A breakthrough dose of approximately 10% of the daily dose every hour as required should be ordered (as it is for pain).

For those not taking opioids and particularly for elderly patients and patients with severe pulmonary disease, it is important to "start low and go slow." Morphine (2.5 to 5.0 mg) or hydromorphone (0.5 to 1.0 mg), both orally every 4 hours, should be initiated and titrated slowly to the most effective dose for controlling dyspnea. The dose that achieves optimal control will vary from patient to patient. When the opioid is started, side effects should be prevented by administering stimulant laxatives and an antiemetic if needed. For patients with mild dyspnea who get symptoms only intermittently or with exertion, small doses of opioids can be used as needed or before exertion.

Most patients with advanced disease are dyspneic at rest and need regular opioid administration.

Opioids should be considered first-line therapy for dyspnea in advanced disease. Second-line agents that have proven useful for dyspnea are neuroleptics, such as chlorpromazine<sup>22</sup> (level II evidence). Anxiolytics have been reported useful, but available evidence does not support their use<sup>23,24</sup> (level II evidence). Suggested doses are shown in **Table 2**.

Some patients get progressively dyspneic as they reach their final day or so of life. If the dyspnea is not managed aggressively, memories of watching someone die gasping for breath will stay with everyone for the rest of their lives. Severe terminal dyspnea is also distressing for health care providers if they do not know how to manage it. It should be managed aggressively with parenteral opioids and sedatives so that patients are breathing comfortably and are moderately sedated (**Table 3**). Physicians should stay with patients and administer medications until the extreme distress is relieved. If a patient has not been taking opioids, as in the case of a sudden obstructing pulmonary embolus, small parenteral doses (2.5 to 5.0 mg) should be given and the effect observed. Parenteral opioid doses can be

**Table 2. Medications used in dyspnea of advanced disease**

**FIRST-LINE MEDICATIONS: OPIOIDS**

For patients already taking opioids regularly, increase dose by 25%-50%.

For patients not taking opioids, who are elderly or have severe chronic obstructive pulmonary disease:

- Morphine: 2.5-5.0 mg by mouth every 4 hours
- Hydromorphone: 0.5-1.0 mg by mouth every 4 hours
- Oxycodone: 2.5-5.0 mg by mouth every 4 hours
- For breakthrough dyspnea, give 10%-20% of daily dose by mouth every hour as needed. Titrate dose by increasing by 25%-50% every 24 hours until symptom controlled.

Younger patients may use double the starting dose.

- Titrate by 25%-50% every 24 hours until symptom controlled.
- Breakthrough dose is the same.

**ADJUVANT MEDICATIONS: NEUROLEPTICS**

- Methotrimeprazine: 2.5-10.0 mg by mouth or subcutaneously every 6-8 hours as needed or regularly
- Chlorpromazine: 7.5-25.0 mg by mouth or subcutaneously every 6-8 hours as needed or regularly

**ADJUVANT MEDICATIONS: ANXIOLYTICS**

- Lorazepam: 0.5-1.0 mg every 4-12 hours as needed and titrate to effect

**Table 3. Management of severe dyspnea in the last hours of life**

Physician should be at bedside

## Opioids

- Must be administered parenterally
- For patients not currently taking opioids: 2.5-5.0 mg IV or SC immediately. For opioid-tolerant patients, increase current dose 50%-100% and administer immediately
- Reassess effect every 10 minutes (IV route) or 20 minutes (SC route)
- Administer opioid infusion if dyspnea likely to be ongoing
- Give methotrimeprazine: 2.5-10.0 mg SC immediately

If patient is severely agitated, sedate with

- Midazolam (2.5-5.0 mg IV/SC) and titrate to effect
- Lorazepam (0.5-1.0 mg IV/SC) and titrate to effect

Use clinical judgement to titrate doses to achieve comfortable breathing and moderate sedation

Call palliative care colleague for help if you have not had experience with this before

IV—intravenous, SC—subcutaneous.

increased by 25% to 50% every 10 minutes (intravenous [IV] route) or 20 minutes (subcutaneous [SC] route) until dyspnea begins to improve. For those already taking opioids, dosage can be increased by 50% to 100% every 10 minutes (IV route) or 20 minutes (SC route).

If severe dyspnea is likely to continue, an opioid infusion could be used once it begins to resolve. In addition to opioids, patients should be given parenteral methotrimeprazine for sedation and relief of dyspnea. If this is not sedating enough, midazolam or lorazepam parenterally will relieve the agitation associated with severe dyspnea. It is not unusual for large doses of opioids and sedatives to be needed to make patients comfortable. The intent is sedation and relief of dyspnea, not hastening death, even though death is likely close due to rapid respiratory failure from disease. Because this degree of dyspnea is rare, physicians who do not have experience with it could call a palliative care colleague for help or dosage recommendations.

**Complementary and alternative treatments.**

A systematic review (level I evidence) of complementary and alternative therapies for dyspnea in advanced illness has revealed that acupuncture and acupressure have great benefit.<sup>25</sup> The same study confirmed that relaxation therapies and counseling were also beneficial.

Mr Charles was prescribed 0.5 mg of hydromorphone orally every 4 hours. This reduced his dyspnea to 5-6/10. The opioid was slowly titrated up to 2 mg every 4 hours, and then the medication was changed to a long-acting hydromorphone (6 mg every 12 hours). A breakthrough dose of 0.5 to 1.0 mg every hour SC or orally was available if needed. Methotrimeprazine (2.5 mg) at bedtime was added to improve his sleep and dyspnea during the night. Mr Charles reported his dyspnea to be 2-3/10 for most of the day. His exacerbations were less frequent and severe and responded to the SC hydromorphone. Three weeks later, he developed a lowered level of consciousness and a weak cough. Pneumonia was diagnosed, but he and his family had decided previously that no further interventions were appropriate. Hydromorphone and methotrimeprazine were administered SC, and he died 2 days later with his family at his bedside.

**Conclusion**

Dyspnea in advanced disease is common and causes substantial suffering. Patients' reports of symptom severity is the best measure. Dyspnea is not related to oxygen saturation or other respiratory measurements. Oxygen is not indicated unless patients find it improves their dyspnea. Opioids relieve dyspnea and are indicated as first-line treatment in dyspnea of advanced disease of any cause. Neuroleptics are helpful adjuvant medications. Communication with patients and their families about end-of-life issues makes them more comfortable and ensures that the goals of care providers are congruent with the goals of patients. ♦

**Competing interests**

None declared

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**CME****An approach to dyspnea in advanced disease**

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**Editor's key points**

- Dyspnea causes great suffering among patients with terminal illness.
- Efficacious measures include keeping the room cool and fairly humid and placing a fan with the air blowing in the direction of the patient's face. Oxygen therapy is not indicated unless patients say it makes them feel better.
- Opioids are first-line treatment for dyspnea. The fear some physicians have of depressing respiratory centres and shortening life are not justified.
- Anxiolytics (lorazepam and midazolam) and neuroleptics (methotrimeprazine and chlorpromazine) can also be useful.

**Points de repère du rédacteur**

- La dyspnée est une source importante de souffrance chez les patients en phase terminale.
- Garder la température de la pièce fraîche avec un bon niveau d'humidité et mettre un ventilateur avec de l'air soufflant en direction du visage du patient sont des mesures efficaces. L'oxygénothérapie n'est pas indiquée à moins que le patient se dise soulagé par cette intervention.
- Les narcotiques sont les médicaments de première ligne pour soulager la dyspnée. Les craintes de certains cliniciens de déprimer les centres respiratoires et d'abrèger la vie ne sont pas justifiées.
- Les anxiolytiques (lorazépam et midazolam) et les neuroleptiques (méthotriméprazine et chlorpromazine) peuvent également être utiles.