Dyspnoea or breathlessness is defined by the American Thoracic Society as “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity” (1). It is highly prevalent in patients with lung cancer, heart failure and chronic obstructive pulmonary disease, three of the most common illness worldwide. Patients with life-limiting cardio-respiratory illnesses have higher intensity of breathlessness for the last three months of life than patients with primary and secondary lung cancer, but breathlessness severity increases in both groups of patients on the last weeks of the life (2,3). Thus, prevalence and severity of dyspnoea escalate significantly as death approaches regardless of underlying life-limiting diseases.

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Dyspnoea is mostly multifactorial, with the symptom resulting from the interaction of physiological, psychological, social, and environmental factors. Therefore, patients undergo a situation of total dyspnoea, concept that describes the patient's experience from multiple perspectives (physical, psychological, interpersonal, and existential) that, synergistically, combine to configure the symptom and to determine its impact (4).

Several studies and reviews have been carried on in the last years to characterize the dyspnoea phenomenon (5-12). Two different patterns of breathlessness have been identified: chronic or continuous breathlessness and breathlessness crisis (acute, incident, episodic, breakthrough breathlessness). Meta-analysis and systematic reviews prove that opioids are beneficial in either opioid-naïve or -tolerant patients. However, data from two recent randomised controlled trials were not able to show the effectiveness of fentanyl for the relief of exertion-induced dyspnoea.

Keywords: Fentanyl; opioids; dyspnoea; advanced cancer; palliative care

Abstract: Two different patterns of breathlessness have been identified: chronic or continuous breathlessness and breathlessness crisis (acute, incident, episodic, breakthrough breathlessness). Meta-analysis and systematic reviews prove that opioids are beneficial in either opioid-naïve or -tolerant patients. However, data from two recent randomised controlled trials were not able to show the effectiveness of fentanyl for the relief of exertion-induced dyspnoea.

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Editorial

Fentanyl for episodic dyspnoea in cancer patients

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Dyspnoea or breathlessness is defined by the American Thoracic Society as “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity” (1). It is highly prevalent in patients with lung cancer, heart failure and chronic obstructive pulmonary disease, three of the most common illness worldwide. Patients with life-limiting cardio-respiratory illnesses have higher intensity of breathlessness for the last three months of life than patients with primary and secondary lung cancer, but breathlessness severity increases in both groups of patients on the last weeks of the life (2,3). Thus, prevalence and severity of dyspnoea escalate significantly as death approaches regardless of underlying life-limiting diseases.

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Several studies and reviews have been carried on in the last years to characterize the dyspnoea phenomenon (5-12). Two different patterns of breathlessness have been identified: chronic or continuous breathlessness and breathlessness crisis (acute, incident, episodic, breakthrough breathlessness). These dyspnoea crises are defined as a “clinically significant aggravation of dyspnoea in patients with continuous dyspnoea or occurring intermittently without constant breathlessness”. Episodic or breakthrough dyspnoea is characterized by a sudden increase of breathlessness intensity with a short duration (7-11).

The first principle of dyspnoea management is to optimize the therapy of any underlying conditions and reversible causes (such as cardio-respiratory diseases or complications, anaemia, primary or secondary lung cancer, muscle weakness, and psychological factors) that might cause or worsen the symptom. The symptomatic management of dyspnoea include pharmacological and non-pharmacological treatments (6,12-17).

Palliative pharmacological treatments of refractory dyspnoea include opioids, benzodiazepines, nebulised furosemide, selective serotonin reuptake inhibitors, and promethazine. Meta-analysis and systematic reviews prove that opioids, especially morphine and diamorphine, are beneficial in either opioid-naïve or -tolerant patients, providing the dose escalation a better response. However, there is no strong evidence on the efficacy of other opioids or other routes of opioid administration for the alleviation of dyspnoea (6,12-17).

Fentanyl is a potent µ-opioid with an evidence base for the treatment of pain. Its advantages against other opioids are its easy transdermal administration, the quick onset action of its transmucosal and intranasal formulations and its low toxicity on renal failure. An improved knowledge of
the efficacy of fentanyl may help to better manage dyspnea in patients with ingest limitations or with impaired renal function. On the other hand, the rapid-onset transmucosal and intranasal fentanyl could be selected as a more suitable treatment for breakthrough breathlessness than oral opioids.

Pinna et al. (18) evaluated fentanyl efficacy in exertion dyspnea in patients with advanced cancer. They conducted a phase II randomized, double-blind, crossover, placebo controlled trial in 13 patients with an average intensity of exercise-induced dyspnoea ≥3/10 on a Numeric Rating Scale (NRS). Eleven males and two females, with a mean age of 65 years, were enrolled from an outpatient palliative care unit in Spain. Sample was designed for a two-tailed α of 0.05 and 80% statistical power. The six-minute walk test (6MWT) was used as trigger of exertion dyspnoea, and changes in breathlessness intensity, on a NRS, were assessed at 3 and 6 min walking, and 30 and 60 minutes after the end of the test. Other variables analysed were changes in oxygen saturation and distance walked during the test; side effects developed and treatment preference of the patients. Fifteen minutes before test, opioid naïve or tolerant-patients received 200 or 400 µg of oral transmucosal fentanyl citrate, respectively, or placebo. Comparison between fentanyl and placebo proved no statistically significant differences in any of the outcome measures.

Findings from Pinna et al. research (18) could be interpreted in different ways. First, fentanyl is not efficacious in breathlessness. Second, fentanyl does not relief exertion breathlessness or its efficacy depends on doses used. Third, opioids could not be beneficial to exercise-induced dyspnoea.

Simon et al. (17) performed a systematic review to evaluate the evidence of fentanyl efficacy for the amelioration of dyspnoea. They included in their review 13 studies: two randomized controlled trials (one only included two patients), two before-after studies and nine case studies. In total were evaluated 88 patients (14 suffering from COPD and 74 with cancer), from all the studies. The administration routes were nebulized fentanyl (70 patients), OTFC (nine patients) and intranasal fentanyl (n=5). Two case reports evaluated transdermal administration of fentanyl (n=3). None of the studies reported respiratory depression or decreases in oxygen saturation despite diverse doses were tested. Notwithstanding all studies described an improvement of breathlessness, the evidence for the fentanyl effectiveness is low because of methodological limitations of the studies. Moreover, the reviewers could not obtain information about the efficacy of fentanyl on the different types of dyspnoea, that is, continuous, induced or breakthrough breathlessness.

Recently, Hui et al. (19) reported, after Simon’s systematic review, their findings on fentanyl effect on exercise-induced breathlessness. The study was designed to evaluate the practicability of conducting a randomized controlled trial of subcutaneous fentanyl for breakthrough dyspnoea in patients with cancer. Twenty two cancer patients with breakthrough breathlessness ≥3/10, Karnofsky Performance Status score of 50% or more, and a stable dose of strong opioids were enrolled in the trial. They also used the 6MWT as trigger of exertion induced dyspnoea, and evaluated changes in breathlessness intensity, on a NRS, Borg fatigue scale, respiratory rate and oxygen saturation, at the end of the test. Patients received subcutaneous fentanyl (between 15% and 25% of morphine equivalent daily dose) or subcutaneous 0.9% normal saline 15 minutes before 6MWT. Subcutaneous fentanyl was associated with significant improvements in outcome measures, but direct comparison between fentanyl and placebo revealed no statistical differences in any measures. Nevertheless, the study was underpowered to detect differences between active and placebo treatment.

As yet, findings of opioids efficacy for incident dyspnoea are insufficient. Only small case series have documented the improvement of dyspnoea episodes with intranasal and oral transmucosal fentanyl (17). On the other hand, the only randomized controlled trial on breakthrough dyspnoea published found no significant difference in dyspnoea relief between systemic hydromorphone, nebulized hydromorphine, and nebulized saline in cancer patients (20).

According to aforementioned studies, patients with chronic breathlessness must be treated with oral or parenteral morphine. Moreover, oral or parenteral morphine, or the rapid-onset formulations of fentanyl, should be used for dyspnoea crises in patients with constant breathlessness. Nevertheless, there are no data to support the routine use of opioids for exercise-induced dyspnoea in patients without chronic breathlessness. Four-registered randomised trials are underway (www.clinical trials.gov) to evaluate the efficacy of different fentanyl formulations for the relief of exercise dyspnoea. Their findings should help us to improve the knowledge of the exercise-induced dyspnoea treatment.

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