





# Unanswered questions and future direction in the management of terminal breathlessness in patients with cancer

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## ABSTRACT

Breathlessness is among the most common and deteriorating symptoms in patients with advanced cancer, which may worsen towards the end of life. Breathlessness in patients with estimated life expectancy of weeks to days has unique clinical features: it tends to worsen rapidly over days to hours as death approaches often despite current symptom control measures. Breathlessness in patients during the last weeks to days of life can be called ‘terminal breathlessness’. While evidence has accumulated for the management of breathlessness in patients with cancer who are not dying, such evidence may not be fully applied to terminal breathlessness. Only a few studies have investigated the best practice of terminal breathlessness in patients with cancer. In this paper, we summarise the current evidence for the management of terminal breathlessness, and propose future directions of clinical research.

## INTRODUCTION

Breathlessness, or dyspnoea, is among the most common and deteriorating symptoms in patients with advanced cancer.<sup>1–5</sup> Breathlessness tends to worsen towards the last weeks to days of life, even with specialist-level palliative care.<sup>3 6 7</sup> Breathlessness in patients during the last weeks to days of life has unique clinical features: it may worsen rapidly over days to hours as death approaches, and is often less responsive to current palliative symptom control measures, therefore at times requiring palliative sedation.<sup>3 6 8</sup> Timely assessment and proactive management of dyspnoea in such patients are of paramount importance. In this paper, we propose the concept of ‘terminal breathlessness’ as compared with a well-defined syndrome of chronic breathlessness, summarise current evidence of its management and discuss future directions of clinical research on terminal breathlessness in patients with cancer.

### Terminology of ‘chronic breathlessness syndrome’ and ‘terminal breathlessness’

Chronic breathlessness syndrome ‘Chronic breathlessness syndrome’ has recently been defined by international experts

as ‘breathlessness that persists despite optimal treatment of the underlying pathophysiology and that results in disability’.<sup>9</sup> The severity of chronic breathlessness can fluctuate over years, and markedly impact on the quality of life.<sup>10 11</sup> Likewise, ‘episodic breathlessness’ has been defined as ‘one form of breathlessness characterized by a severe worsening of breathlessness intensity or unpleasantness beyond usual fluctuations in the patient’s perception’, which can lead to high levels of anxiety.<sup>12</sup> Chronic breathlessness and episodic breathlessness are sometimes discussed as entities equivalent to chronic pain and breakthrough pain, respectively.<sup>12 13</sup> Several randomised controlled trials (RCT) and systematic reviews have been conducted in the management of chronic breathlessness of patients with various diseases.<sup>14–18</sup> A low-dose sustained-release morphine has now been approved for use in the symptomatic reduction of chronic breathlessness in Australia.<sup>19</sup>

### Terminal breathlessness

Prior literature has largely focused on breathlessness specifically in patients who are not dying, and thus, such evidence may not be fully applied to breathlessness in patients with an estimated life expectancy of weeks to days. In the USA, the Medicare criteria for hospice eligibility of patients with advanced lung disease, the ‘terminal stage’ was defined as life expectancy of 6 months or less.<sup>20</sup> In this paper, we tentatively define ‘terminal breathlessness’ (or ‘terminal dyspnea’) as breathlessness in patients with an estimated life expectancy of weeks to days. Similar terminology is also proposed in ‘terminal agitation’ in dying patients, in whom the treatment goal is to relieve agitation rather than to reverse delirium.<sup>21 22</sup>

International guidelines recently recognised breathlessness as a frequent and one of the most distressing symptoms in the

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last phase of life.<sup>23 24</sup> They indicate that the focus of treatment in this phase shifts to pharmacological if existing treatment is insufficient, aggressive symptom relief may be required and human attendance and empathy are paramount.<sup>23 24</sup>

### Measurements of terminal breathlessness

Breathlessness is a subjective sensation by definition, and should ideally be evaluated by patient-reported outcomes. As death approaches, however, subjective assessment can become increasingly challenging, as the level of consciousness tends to inevitably worsen.<sup>6 8</sup> At present, there is no international consensus on how to measure breathlessness subjectively in patients with an impaired communication capacity.

Proxy rating of breathlessness has been used with or without reference to valid and reliable scales (eg, Integrated Palliative care Outcome Scale (IPOS), Support Team Assessment Schedule (STAS))<sup>25 26</sup> as well as objective signs potentially indicating the presence of breathlessness (eg, Respiratory Distress Observation Scale (RDOS)).<sup>27</sup> However, proxy rating may not fully reflect subjective perception. A cross-sectional survey among patients with advanced cancer with breathlessness showed that physiological measures could not reliably inform about patients' expression of breathlessness.<sup>28</sup> For example, the RDOS only had a weak correlation with patients' expression of breathlessness ( $r=0.35$ ).<sup>28</sup> While patients' expression of breathlessness was correlated moderately with family caregivers' ( $r=0.68$ ) and nurses' ( $r=0.50$ ) assessment, families overestimated while nurses underestimated breathlessness compared with patients. Moreover, a proxy rating could be affected by altered end-of-life respiratory patterns, and complicated by coexisting symptoms (eg, pain and anxiety), which could be influenced by treatment such as opioids and sedatives. The identification of biological signs of a perceived sensation of breathlessness at the cerebral level would help evaluate the presence and intensity of breathlessness in non-communicative patients; however, such evaluation has yet to be investigated.

### CURRENT EVIDENCE SUPPORTING TREATMENT FOR TERMINAL BREATHLESSNESS

Few studies have investigated the best practice for patients with cancer with terminal breathlessness, that is, breathlessness in patients with estimated life expectancy of weeks to days. A recent systematic review of literature published until 2016 identified only five studies (two RCTs and three prospective cohort studies) that investigated the effectiveness of drug therapy for breathlessness in the last days of life.<sup>29</sup> Several new papers have since been published.<sup>23 30–32</sup> Below is a summary of available evidence for the main treatment modalities for breathlessness and related conditions in patients with cancer with estimated life expectancy of weeks to days.

### Opioids

#### Morphine

Morphine has been used as the first-line pharmacological therapy for alleviating breathlessness in patients with advanced cancer throughout the world. Multiple clinical guidelines recommend morphine for cancer breathlessness in general.<sup>23 24 31 33</sup> In this situation, the recommendations are based on studies of single-dose administration of morphine involving patients with relatively good condition.<sup>34 35</sup> While these studies showed the efficacy of morphine for cancer breathlessness compared with a placebo, the efficacy of its regular or continuous administration has not been confirmed. In addition, these studies included only cognitively competent patients with cancer with breathlessness. In clinical practice, morphine is widely used in various forms including continuous intravenous/subcutaneous infusion to ensure timely titration, rapid breathlessness relief and the avoidance of unnecessary adverse events in the setting of clinical deterioration and organ dysfunction during the last weeks to days of life.<sup>32 36 37</sup> Thus, it is uncertain whether these results can be applied to patients with cancer who are very close to death.

One preliminary RCT explored the effects of morphine with or without midazolam on breathlessness in patients with cancer whose life expectancy was less than a week.<sup>38</sup> In this study, the investigators compared three treatment regimens (around-the-clock (atc) morphine with midazolam as needed; atc midazolam with morphine as needed; or atc morphine plus midazolam with morphine as needed).<sup>38</sup> Median breathlessness intensity within 48 hours after starting the study medications in the regular morphine group was not significantly different from those in the regular midazolam group. A recent systematic review identified no major safety concerns regarding the use of morphine, other opioids, or midazolam for breathlessness in the dying.<sup>29</sup>

#### Other opioids

No clinical trials have been conducted to confirm the effects of opioids other than morphine on breathlessness in patients with cancer with estimated life expectancy of weeks to days. Clinical guidelines suggest that hydromorphone or oxycodone can be used for breathlessness in patients with advanced cancer as an alternative to morphine, or that opioid doses can be increased by 25% for non-opioid-naïve patients.<sup>23 24 31</sup> However, robust evidence supporting the use of opioids other than morphine for cancer breathlessness in this situation has been lacking and there may not be a class effect.<sup>39</sup> Only one study evaluated the effectiveness of hydromorphone for breathlessness in terminally ill patients with cancer who were admitted to a palliative care unit (mean survival, 22 days).<sup>40</sup> The patients experienced a significant decrease in breathlessness intensity over 2 hours without developing clinically significant respiratory depression. Two retrospective studies examined the effect of oxycodone on breathlessness in patients with cancer close to death.

In one study, breathlessness improved in 39 of 44 patients (88.6%) after the administration of subcutaneous oxycodone infusion.<sup>41</sup> In the other study involving 19 patients with cancer with breathlessness (median survival, 6 days), 68.4% of them showed a response to intravenous oxycodone infusion within 3 days.<sup>30</sup>

Little is known about the effect of fentanyl on breathlessness in patients with cancer with estimated life expectancy of weeks to days. One exploratory observational study examined the effect of intravenous fentanyl on breathlessness in patients with cancer close to death.<sup>42</sup> Although 7 of 16 patients responded to intravenous fentanyl, the study design and high attrition rate precluded any conclusions regarding its effect. Thus, the effects of fentanyl on terminal breathlessness remain unknown.

### Benzodiazepines

It is evident that breathlessness closely interacts with anxiety in patients with advanced cancer.<sup>43 44</sup> Benzodiazepines are anxiolytics, and could thus relieve breathlessness. Like opioids, benzodiazepines have been widely used and recommended in palliating intense symptoms including breathlessness at the end of life.<sup>24 36</sup> A meta-analysis of benzodiazepines for the treatment of patients with cancer breathlessness (not specific for terminal breathlessness) found no significant benefit of benzodiazepines over a placebo or morphine.<sup>45</sup> However, only a few heterogeneous studies were included. Clinical guidelines and international experts suggested that benzodiazepines have additional benefit in palliating breathlessness not responding to opioids in patients with cancer close to death.<sup>23 24 36 46 47</sup> In patients with cancer with estimated life expectancy of weeks or longer, the use of benzodiazepine for breathlessness may need to be limited to those who have been treated with opioids or other interventions, as they could potentially worsen sedation and delirium. In contrast, in patients with cancer with estimated life expectancy of days who suffer from breathlessness not responding to symptomatic treatment, benzodiazepines are often used for palliative sedation.<sup>24 29 47</sup>

Strictly speaking, however, it remains unclear whether benzodiazepines alone are more effective for terminal breathlessness than opioids alone, whether the combination of benzodiazepine plus an opioid is more effective than each of them alone and what types of terminal breathlessness are the appropriate target of benzodiazepines (eg, terminal breathlessness with coexisting anxiety).

### Corticosteroids

An elevated inflammatory response in patients with advanced cancer could contribute to breathlessness.<sup>48</sup> Corticosteroids could thus modulate the sensation of breathlessness with their potent anti-inflammatory activity. The effects of corticosteroids for breathlessness in patients with cancer have been suggested in a pilot RCT, several prospective observational studies and case reports.<sup>49–54</sup> Yet, the indications and doses of

corticosteroids for cancer breathlessness have not been established. Clinical guidelines recommend that corticosteroids be indicated for breathlessness due to specific conditions (eg, lymphangitis carcinomatosa, superior vena cava syndrome and airway obstruction), rather than for breathlessness of any aetiology, based on limited evidence.<sup>24 31</sup>

However, no study has confirmed the effects of corticosteroids on terminal breathlessness. Although corticosteroids are well tolerated by patients with cancer with dyspnoea in general,<sup>55</sup> they may cause psychoactive side effects in patients with cancer during the last weeks to days of life. It remains uncertain whether the effectiveness exceeds their risks in this phase.

### Supplemental oxygen

No evidence exists that supplemental oxygen relieves breathlessness, unless the patient suffers from hypoxia.<sup>56 57</sup> Clinical guidelines essentially recommend oxygen therapy only for breathlessness in patients with hypoxia, although its use may be permissible if subjective relief is reported.<sup>23 24 31</sup> In daily practice, however, oxygen therapy is widely used in the clinical setting of breathlessness in patients with terminal cancer irrespective of the presence of hypoxaemia.<sup>58 59</sup> Balance should be aimed for between the benefit and potential disadvantages of oxygen therapy (eg, being a burdensome intervention requiring tubing and tanks, having to wear a mask when the person may still want to try to speak, the drying effects of oxygen on mucosa), especially in non-hypoxic patients with estimated life expectancy of weeks to days.

One small randomised trial examined the use of bilevel positive airway pressure (BiPAP) and high-flow oxygen therapy in hospitalised patients with advanced cancer. Both modalities were correlated with a significant reduction in breathlessness scores, although there were no differences between the two groups.<sup>60</sup> Another randomised trial compared BiPAP with the venturi mask, and confirmed the benefit for breathlessness, particularly in patients with hypoventilation.<sup>61</sup> Although these modalities may be useful for breathlessness relief if deemed clinically appropriate, not all patients can tolerate them and further research is needed.

### Non-pharmacological treatment

Recent systematic reviews on non-pharmacological interventions for breathlessness relief in patients with advanced diseases showed the effectiveness of fan therapy, neuro-electrical muscle stimulation, chest wall vibration, walking aids, breathing training and holistic services.<sup>62–65</sup> Among these, fan therapy may be readily available for patients with cancer with terminal breathlessness. In a recent parallel-arm RCT that evaluated the effect of fan therapy on breathlessness in 40 terminally ill patients with cancer compared with a fan-to-legs group, the mean breathlessness scores decreased more significantly in the intervention group.<sup>66</sup> A recent meta-analysis also demonstrated the immediate benefit of fan therapy on breathlessness at rest





compared with a control group.<sup>64</sup> As evidence is limited, it is unclear whether non-pharmacological management other than fan therapy is effective for terminal breathlessness. However, patients with terminal breathlessness may benefit from holistic services (eg, breathing therapists, person-centred dignified care) which have recently been shown to reduce distress and improve psychological outcomes in patients with advanced disease and chronic breathlessness.<sup>65</sup>

### Breathlessness not responding to symptomatic treatment

Breathlessness accounts for the majority of end-of-life suffering alongside delirium, for which palliative sedation is one of the therapeutic options.<sup>47 67–70</sup> A benzodiazepine is the most common class of medication prescribed as a sedative in patients who have persistent intractable breathlessness despite the use of opioids.<sup>46 47 67–70</sup>

Guidelines and expert reviews recommend that sedatives should first be titrated to a minimal dose required to provide adequate palliation of suffering, rather than to continuously induce unconsciousness.<sup>71–74</sup> As part of efforts to standardise end-of-life treatment, a reproducible protocol of proportional midazolam use has recently been proposed that reflects the treatment intention and expected outcome.<sup>71 75</sup> However, it remains unknown when breathlessness should be considered non-responding to symptomatic treatment, and how best sedatives should be titrated to relieve persistent intractable breathlessness in particular.

### Other issues in the last days of life

Respiratory secretion, especially death rattle, and changes in respiratory patterns (eg, Cheyne-Stokes breathing and respiration with mandibular movement) are often seen during the last days of life.<sup>8 23 24</sup> These may lead to distress in families; while clinicians have traditionally believed there is no patient distress caused by death rattle and changes in respiratory patterns developed in the context of declining consciousness, whether the patient perceives distress remains controversial.<sup>76–78</sup>

Anticholinergics have been used to reduce respiratory secretion; however, systematic reviews revealed no additional benefit of medications or non-pharmacological treatments compared with a placebo.<sup>79 80</sup> A prophylactic use of anticholinergics has recently been proposed to prevent death rattle but such a suggestion is without sufficient evidence of benefit.<sup>77</sup> Therefore, the evidence for pharmacological management to reduce secretions is controversial at present. Repositioning of the patients and oropharyngeal suctioning can be effective if gently performed, but could cause discomfort in imminently dying patients.<sup>81</sup> Educating family caregivers is of paramount importance.<sup>78</sup>

### UNANSWERED RESEARCH QUESTIONS IN TERMINAL BREATHLESSNESS

As mentioned above, numerous clinical questions have yet to be answered regarding the assessment and treatment of

patients with terminal breathlessness. This may be in part because terminal breathlessness has not necessarily been regarded as a symptom with unique features, and because conducting clinical trials involving patients with an estimated life expectancy of weeks to days is challenging due to practical and ethical concerns.

However, recent international efforts have paved the way towards building high-quality evidence in the management of previously ill-defined symptoms or discomfort in this population. For example, a consensus definition of chronic breathlessness syndrome has widely raised recognition of this hidden discomfort, and led to a number of clinical trials with various treatment modalities.<sup>9 14–18</sup> In addition, recent studies on terminal agitation and death rattle have demonstrated the feasibility of RCTs in patients during the last days of life, if appropriate strategies are implemented.<sup>22 77 82</sup> Strategies include, but are not limited to, the use of advance or proxy consent, standardisation of care programmes, the application of short observation periods and the use of clinically implemented outcomes.<sup>22 75 82</sup> While an RCT is the gold standard for demonstrating the efficacy of medication, continuous recording of routinely collected data would also enable researchers to conduct non-randomised comparative studies among treatment modalities. Below are unanswered questions and potential strategies to promote future research in terminal breathlessness (table 1).

#### What is the definition of terminal breathlessness?

Although widely referred to in clinical guidelines and systematic reviews, terminal breathlessness has not been formally defined.<sup>23 24 29</sup> We herein propose a tentative definition of terminal breathlessness, that is, 'breathlessness in patients with estimated life expectancy of weeks to days'. However, this may require further refinement by international experts.

#### How should we measure symptom intensity and patient discomfort related to terminal breathlessness?

From a pragmatic viewpoint, patient-reported outcomes (eg, breathlessness numerical rating scale (NRS), visual analogue scale, modified Borg scale) should be obtained as much as possible. If patient-reported assessment is not available as death approaches, then caregiver proxy rating (eg, NRS, IPOS, STAS) might be a reasonable alternative. In addition to caregivers' proxy assessment, validated objective measurements by clinicians (eg, RDOS or Discomfort Scale for Dementia of the Alzheimer's Type in pain and other discomfort assessment) could be used, although the correlation between patients' subjective assessment of breathlessness and physiological findings is not established.<sup>83</sup> A gold standard of breathlessness assessment in non-communicative patients should be urgently established.

#### Are opioids and other treatment modalities effective and safe for terminal breathlessness?

Only a few prior studies explored the effects of morphine, other opioids and benzodiazepines for terminal

**Table 1** Research questions regarding terminal breathlessness and future directions

Major research questions	Strategies (examples)
1. What is the definition of terminal breathlessness?	▶ Conduct a Delphi study or organise taskforce discussions to achieve consensus on the definition of terminal breathlessness by international experts.
2. How should we measure symptom intensity and patient discomfort related to terminal breathlessness?	▶ Use patient-reported outcomes (eg, breathlessness NRS, VAS, modified Borg scale) as much as possible. ▶ Examine if the existing proxy rating scales (eg, NRS, IPOS, STAS, RDOS) are sufficient for cognitively impaired patients with terminal breathlessness; if not, seek a consensus on more valid and reliable proxy rating.
3. Are opioids and other treatment modalities effective and safe for terminal breathlessness?	▶ Conduct RCTs to examine the efficacy and safety of morphine and other opioids in the form of continuous infusion, parenteral benzodiazepines and corticosteroids (eg, parenteral morphine vs placebo; oxycodone vs placebo; hydromorphone vs placebo; corticosteroids vs placebo; or the comparison among these medications).
4. How should parenteral opioids be titrated, and does an upper limit of opioids exist for terminal breathlessness?	▶ Conduct RCTs comparing rapid versus slow titration, as well as morphine increment versus morphine plus midazolam for breathlessness refractory to low-dose morphine. ▶ Conduct a dose-finding study to clarify the effective and maximal dose of opioids.
5. Which patients benefit the most from treatment for terminal breathlessness?	▶ Conduct a large prospective cohort study to identify factors contributing to the response to or adverse events of opioids and other treatment modalities.
6. What non-pharmacological management is most effective for terminal breathlessness?	▶ Conduct RCTs to explore the efficacy and adverse events of oxygen therapy for terminal breathlessness in patients with cancer with or without hypoxaemia. ▶ Identify effective and feasible non-pharmacological modalities for terminal breathlessness other than fan therapy, and use non-pharmacological management as part of a multifaceted approach to patients with terminal breathlessness.
7. How should we define terminal breathlessness treatment goals and manage it if such goals are not achieved?	▶ Explore if personalised breathlessness goals that balance both breathlessness relief and maintenance of consciousness can be developed.
8. Are there promising novel treatment modalities for terminal breathlessness?	▶ Explore the benefit of novel medications (eg, sedatives). ▶ Collaborate with basic scientists to obtain more insights into the pathophysiology and modulators of the perception of terminal breathlessness, predictors of the treatment response and biologically targeted treatment.
9. How should family distress related to terminal breathlessness be managed?	▶ Conduct qualitative studies to identify in-depth experiences of families caring for patients with terminal breathlessness. ▶ Develop comprehensive interventions (eg, education, support) for family caregivers caring for patients with terminal breathlessness.

IPOS, Integrated Palliative care Outcome Scale; NRS, numerical rating scale; RCT, randomised controlled trial; RDOS, Respiratory Distress Observation Scale; STAS, Support Team Assessment Schedule; VAS, visual analogue scale.

breathlessness. Future high-quality RCTs should urgently examine the efficacy and safety of widely used modalities (eg, morphine and other opioids, benzodiazepines, and corticosteroids), as well as their psychoactive effects in the setting of declining consciousness in imminently dying patients with cancer with breathlessness.

#### How should opioids be titrated, and does an upper limit of opioids exist for terminal breathlessness?

Although the efficacy of opioids for cancer breathlessness has been demonstrated, how best to start and titrate them for terminal breathlessness remains unclear. Unlike chronic breathlessness where a majority of patients achieve breathlessness relief with low-dose sustained-release morphine orally (eg, 10–30 mg/day on a weekly titration),<sup>84</sup> terminal breathlessness often requires the

rapid titration of opioids.<sup>36</sup> A systematic review of dose titration of opioids for cancer pain also revealed only limited evidence, and indicated that parenteral titration is more effective if it is important to achieve rapid symptom control (within hours).<sup>85</sup>

This lack of evidence results in a wide variability in the practice of treating patients with terminal breathlessness among palliative care specialists.<sup>32–37</sup> A number of important clinical questions have yet to be answered. How should opioids be titrated orally or parenterally? How much should opioids be given as a rescue dose, and how frequently? What is the upper limit of opioids for terminal breathlessness? What pharmacological treatment should be offered when further opioid titration is deemed controversial due to the emergence of adverse

events? All of these should be empirically confirmed by future studies such as prospective dose-finding studies and RCTs.

### **Which patients benefit the most from treatment for terminal breathlessness?**

Preliminary evidence indicated that approximately 40%–90% of patients with terminal breathlessness achieved symptom relief 24 hours following the administration of parenteral opioids and/or midazolam.<sup>38</sup> The rest of them continued to suffer breathlessness, had a decline in consciousness, or died. The predictors of the response to opioids remain largely unknown. A large prospective cohort study will be warranted to identify factors contributing to the response or adverse events of opioids and other treatment modalities.

### **What non-pharmacological management is most effective for terminal breathlessness?**

Fan therapy is an easy, evidence-based non-pharmacological management for breathlessness in dying patients with cancer.<sup>64</sup> As death approaches, however, holding a fan may become more burdensome. Supplemental oxygen might be a good alternative in gently stimulating  $V_3$  areas, even if no hypoxia is noted; however, there is a dearth of literature to support/refute the use of supplemental oxygen in this setting. Moreover, clinical trials are warranted to explore the efficacy and adverse events of oxygen therapy for terminal breathlessness in patients with cancer irrespective of the presence of hypoxaemia. Effective and feasible non-pharmacological modalities for terminal breathlessness other than fan and oxygen therapy should also be identified, and used as part of a multifaceted approach to patients with terminal breathlessness.

### **How should we define terminal breathlessness treatment goals and manage it if such goals are not achieved?**

Most patients wish to have symptom relief and remain mentally aware at the end of life.<sup>86</sup> However, imminently dying patients tend to show a decline in consciousness associated with organ dysfunction as part of the natural dying process, irrespective of the use of opioids and/or sedatives.<sup>6 8 32</sup> In addition, terminal breathlessness may become refractory to standard symptom management, and sometimes require palliative sedation. Thus, the management of terminal breathlessness needs to take into account a delicate balance of trade-off between breathlessness relief and maintenance of consciousness.<sup>32</sup> Best balance of the trade-off highly depends on patients' goals and preferences. For example, imminently dying patients waiting for family members who live far away to arrive may want to minimise the use of medications with sedative effects, whereas those who prioritise physical comfort may ask clinicians to maximise the use of medications for symptom control even if there is a risk of losing consciousness.

To provide goal-concordant care, individuals' goals and needs for further treatment should be clarified by patients themselves or their loved ones if their consciousness level has declined. How to measure personalised symptom goals needs to be established.<sup>87</sup>

### **Are there promising novel treatment modalities for terminal breathlessness?**

Very few medications other than opioids and midazolam have been demonstrated to be effective for patients with terminal breathlessness. The net benefit of breathlessness treatment might be limited with the optimisation of existing modalities alone. To achieve more efficient breathlessness relief, novel modalities should be explored.

Basic science has begun to explore factors contributing to the response to opioids. For example, a recent exploratory study in palliative care patients on opioids identified a biologically plausible single nucleotide polymorphism that was associated with breathlessness intensity.<sup>88</sup> However, it remains unclear if interventions with efficacy in patients with a life expectancy of months can be applied with similar efficacy in patients with terminal breathlessness in whom pharmacokinetics of medications and goals of care may differ. Future development of basic science and translational research are warranted to obtain more insights into pathophysiology and modulators of perception of terminal breathlessness, predictors of treatment response and biologically targeted treatment.

### **How should family distress related to terminal breathlessness be managed?**

A bereaved family survey indicated that families feel less necessity of improvement if the clinicians had ensured their loved one's comfort and coached the family on how to care for the patient.<sup>89</sup> Qualitative studies can identify in-depth experiences of families caring for patients with terminal breathlessness. Comprehensive interventions (eg, education, support) for family caregivers of patients with terminal breathlessness might enhance families' self-efficacy, relieve their distress and help patients and families spend the last days of life as they desire.

## **CONCLUSION**

In conclusion, there is little evidence to support the concept, assessment and management of terminal breathlessness in patients with cancer. Future research is urgently needed to define, measure and manage terminal breathlessness, which would allow patients to express their hopes regarding care and engage in decision-making at the end of life; families to provide informal support; clinicians to closely monitor and provide necessary treatment; researchers to develop appropriate treatment strategies; and health services to implement care pathways to achieve patient goals effectively.

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