Practice Review: Pharmacological management of severe chronic breathlessness in adults with advanced life-limiting diseases

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Simon ST, Higginson IJ, Bausewein C, et al., Practice review: Pharmacological management of severe chronic breathlessness in adults with advanced life-limiting diseases. Palliative Medicine. Copyright © 2024 The Author(s). DOI: https://doi.org/10.1177/02692163241270945.

Abstract

Background: Severe and refractory chronic breathlessness is a common and burdensome symptom in patients with advanced life-limiting disease. Its clinical management is challenging because of the lack of effective interventions.

Aim: To provide practice recommendations on the safe use of pharmacological therapies for severe chronic breathlessness.

Design: Scoping review of (inter)national guidelines and systematic reviews. We additionally searched for primary studies where no systematic review could be identified. Consensus on the recommendations was reached by 75% approval within an international expert panel.

Data sources: Searches in MEDLINE, Cochrane Library and Guideline International Network until March 2023. Inclusion of publications on the use of antidepressants, benzodiazepines, opioids, or corticosteroids for chronic breathlessness in adults with cancer, chronic obstructive pulmonary disease, interstitial lung disease, or chronic heart failure.

Results: Overall, the evidence from eight guidelines, 14 systematic reviews and 3 RCTs on antidepressants is limited. There is low quality evidence favouring opioids in patients with chronic obstructive pulmonary disease, cancer, and interstitial lung disease. For chronic heart failure, evidence is inconclusive. Benzodiazepines should only be considered for anxiety associated with severe breathlessness. Antidepressants and corticosteroids should not be used.

Conclusion: Management of breathlessness remains challenging with only few pharmacological options with limited and partially conflicting evidence. Therefore, pharmacological treatment should be reserved for patients with advanced disease under monitoring of side effects, after optimisation of the underlying condition and use of evidence-based non-pharmacological interventions as first-line treatment.

Keywords

Dyspnea, breathlessness, opioids, antidepressive agents, steroids, benzodiazepines, drug therapy, palliative care

What is already known about the topic?

- Chronic breathlessness is a common symptom in patients with advanced disease.
- Chronic breathlessness is often not adequately treated.
- Routine use of pharmacological treatments to manage breathlessness is associated with increased morbidity and mortality.

What this paper adds?

- Based on the current literature, the evidence for the use of pharmacological interventions for the relief of breathlessness is weak – including opioids, benzodiazepines, antidepressants, and corticosteroids.
- The use of pharmacological options should be carefully weighed between benefit and harm.
- This underpins the importance to optimize the underlying condition which causes breathlessness and to use non-pharmacological options as first-line treatment.

Implications for practice, theory or policy

- Before starting pharmacological measures for the symptomatic relief of chronic breathlessness, a staged approach should be implemented after optimizing the underlying disease(s) and using non-pharmacological interventions as first-line treatment options.
- Opioids are the only drugs with some, albeit weak and conflicting evidence in clinical trials and should therefore be used with caution and in low dose.
- Benzodiazepines should be considered only for selected patients if the predominant symptom is anxiety/panic associated with severe, refractory breathlessness, while antidepressants and corticosteroids should not be used for the relief of chronic breathlessness.

Background

Breathlessness that ‘‘persists despite optimal treatment of the underlying pathophysiology and that results in disability’’, is referred to as chronic breathlessness syndrome.[1] Chronic breathlessness is one of the most common, burdensome, and neglected symptoms affecting patients with life-limiting diseases and in end-of-life care and represents a major clinical challenge.[2–5]

Non-pharmacological treatments and management strategies are helpful,[6] but their usage is not always possible or sufficiently effective to relieve breathlessness, e.g. in the dying phase. The use of pharmacologic treatment options for chronic breathlessness currently varies widely. Therefore, an evidence-based guideline is needed.[7]

Our aim is to provide recommendations for the safe symptomatic management of chronic breathlessness based on the state of evidence and best clinical practice on the use of antidepressants, benzodiazepines, opioids, and corticosteroids in adult patients with advanced stages of cancer, chronic heart failure (CHF), interstitial lung disease (ILD), or chronic obstructive lung disease (COPD), and to identify gaps where further research is needed. Hereby, it is important to weigh benefit and harm and to pursue a careful and responsible prescribing without harmful adverse effects.

Methods

We conducted this practice review following a scoping review methodology[8] to identify guidelines and systematic reviews on the use of antidepressants, benzodiazepines, opioids, and corticosteroids for the relief of chronic breathlessness in adult patients with cancer, COPD, ILD, or chronic heart failure (CHF) (see search strategy, Supplement 1), as these conditions represent the main causes of severe and refractory chronic breathlessness. For reporting the results, we followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist.[9] Guidelines were searched via Guidelines International Network (GIN) and Medline (Pubmed) from 2017 to 17 March 2023, and were included if published by a national or international body and not older than five years (2018 – 2023) to ensure their relevance. Systematic reviews had to be not older than 10 years, as we aimed to identify more recent evidence. Therefore, the search in the Cochrane Library and Medline (Pubmed) was limited from January 2013 to 20 March 2023. An additional search for primary studies was conducted where no systematic review were identified, searching the Cochrane Central Register of Controlled Trials (CENTRAL) and Medline (Pubmed) for primary studies with original data, except case series in adult patients with cancer, COPD, ILD, or chronic heart failure (CHF). Additionally, guidelines, systematic reviews, and primary studies known by the expert panel were included if fulfilling the inclusion criteria. All guidelines, systematic reviews, and primary studies were independently screened by three researchers on inclusion (CW, AP, STS).

Based on the identified evidence, the authors drafted recommendations, allocated them to the categories “Do”, “Don’t” and “Don’t know”[10] and determined the strength of recommendation (see Table 1). The recommendations were subsequently agreed upon via an online survey tool (LimeSurvey©) sent to a panel of 20 international clinical experts and patient representatives. All experts had scientific and clinical experience and expertise in research and management of chronic breathlessness with a wide range and diversity regarding age, sex, and country of origin, and all were part of the BETTER-B consortium (EU funded research programme on chronic breathlessness with 13 international partners). 75% of votes were required to achieve a consensus on recommendations.

Table 1. Recommendation categories and criteria for strength of recommendations

Evidence	
Do	recommendations for practice that can be made with a supporting body of evidence for effectiveness or efficiency
Do not	recommendations against activities for which there is a supporting body of evidence to show inefficiency, ineffectiveness, or indeed harm.
Don't know	should be identified areas for further research as there is either an absence of evidence or the current evidence is unclear or not of convincing quality or rigour. Don't knows should be expressed as questions which if answered through further research would have an impact on clinical practice.
Strength of recommendations	
Strong	A large and consistent body of evidence, such as a systematic review
Moderate	Solid empiric evidence from one or more papers plus the consensus of the authors
Tentative	Limited empiric evidence plus the consensus of the authors

Results

Eight international guidelines and fourteen systematic reviews, as well as three RCTs on the use of antidepressants were included (see PRISMA chart, Supplement 2, and included studies, Supplement 3). The consensus process included two online-consensus rounds and a final hybrid conference of the expert panel. All recommendations reached at least 75% agreement and are presented in Table 2.

Table 2. Summary of recommendations on the pharmacological management of chronic breathlessness

	Recommendation	**Strength of recommendation**
A staged approach to the management of severe, chronic breathlessness should be adopted*. This includes: • Optimisation of the underlying condition, comorbidities and exacerbating factors wherever possible in accordance with the wishes of the patient • Non-pharmacological interventions: ➢ Use of evidence-based non-pharmacological interventions as first-line treatment, if indicated ➢ Monitoring of the effect of non-pharmacological interventions whether they provide sufficient symptom relief		
Do	Pharmacological interventions: if no sufficient relief is achieved by non-pharmacological interventions, consider carefully adding pharmacological options for patients with advanced disease	
	1. Opioids	
	(a) Consider regular low-dose opioids titrated against effect for patients with severe, refractory breathlessness in COPD, cancer, or ILD	Tentative
	(b) Where possible, use modified release (slow release) formulation	Tentative
	(c) Reduce dose and/or increase dosing interval for renal failure ~~and consider alternatives such as fentanyl~~	Moderate
	(d) Start laxatives for the prophylaxis and treatment of constipation if indicated	Strong
	(e) Consider anticipatory treatment for nausea/vomiting as a side effect	Moderate

	(f) Monitor for adverse effects such as respiratory failure or drug dependence and/or withdrawal symptoms	Moderate
	2. Benzodiazepines	
	(a) Consider benzodiazepines only if the predominant symptom is anxiety/panic associated with severe, refractory breathlessness	Tentative
	(b) Monitor adverse effects carefully such as sedation, increased tendency to fall, paradoxical effect, drug dependence and/or withdrawal symptoms	Strong
	3. Only in the last days of life (dying phase), consider the combination of opioids and benzodiazepines when the relief of severe, refractory breathlessness (and maybe anxiety) cannot be achieved otherwise	Tentative
Do not …	1. … routinely use pharmacological treatment as first-line treatment unless the patient is in the last days of life	Moderate
	2. … routinely use doses of opioids >30mg morphine equivalent/24hrs in patients with COPD	Moderate
	3… routinely use benzodiazepines >1mg lorazepam equivalent/24 hrs and avoid long-term use unless there is clear evidence of individual patient benefit	Moderate
	4. … routinely use corticosteroids for the relief of chronic breathlessness unless there is clear evidence of individual patient benefit	Tentative
	5. … use antidepressants for the relief of chronic breathlessness	Strong
	6. … routinely use pharmacological treatment for known breathlessness episodes with an onset of effect longer than the breathlessness episode lasts	Strong
Don't know if there is a benefit or harm of	1. Opioids for the relief of chronic breathlessness in patients with chronic heart failure (CHF)	
Footnote: *In exceptional situations, i.e. when a patient is experiencing extreme distress or is entering the dying phase, pharmacological interventions can be necessary as a first step (alongside non-pharmacological interventions i.e. calming or breathing techniques).		

Overall, the evidence for the use of pharmacological therapies in the management of chronic breathlessness is weak. Therefore, due to potential side effects of drugs, evidence-based non-pharmacological options should be considered as first-line treatment. This can be operationalised by adopting a staged approach, with thorough assessment of the effect of each treatment step in relieving severe chronic breathlessness.[6] If the treatment of reversible causes by optimising the underlying condition, comorbidities and exacerbating factors as a first step does not lead to a satisfactory relief, non-pharmacological interventions should be started in a second step. Third, if these have an insufficient effect, consider introducing additionally any pharmacological treatment carefully, with constant awareness of possible side effects and adverse events (simultaneous use of pharmacological and non-pharmacological interventions).

In exceptional situations to achieve rapid relief, ~~i.e. when a patient is experiencing extreme distress or is entering the dying phase,~~ pharmacological interventions can be necessary as a first step (alongside non-pharmacological interventions i.e. calming or breathing techniques).[6] This might be the case when a patient is experiencing extreme distress or is entering the dying phase.

International guidelines recommend optimizing the underlying condition, comorbidities and exacerbating factors as first stage to relieve severe chronic breathlessness.[6,11] This includes treatment of cancer, COPD ILD, and CHF. Further reversible causal conditions should be optimally treated, e.g. infection, pleural effusion, anaemia etc.[6,11]

Breathlessness is to be considered as a syndrome, including various influencing factors and comorbidities such as anxiety and depression, social and environmental factors. Consequently, a thorough and holistic multidisciplinary assessment will help to better delineate which treatment options should be best implemented, taking into account the complexity of the syndrome.

Many evidence-based non-pharmacological interventions have shown effective relief of chronic and acute breathlessness and are thus recommended in clinical guidelines.[6,11] These improve self-management and reassurance, have a low risk of harm, and can be used easily after training by most patients. Recommended non-pharmacological interventions include for example calming, breathing techniques, positioning, walking aids or hand-held fan.[6,12,13]

Ask the patient if the intervention used provides sufficient relief.[6,11] If not, check if the patient uses the technique correctly or needs additional training. Consider to combine different non-pharmacological interventions to achieve adequate relief. Most of the non-pharmacological interventions need training and time until they can be used to a satisfactory degree, as stated in recent literature.[14–16]

Practice Recommendations 'Do'

If no sufficient relief is achieved by non-pharmacological interventions, consider carefully adding pharmacological options for patients in advanced disease

If there is insufficient symptom relief, international guidelines recommend to consider starting pharmacological treatment carefully.[6,11] Pharmacological treatment should be reserved for patients in late-stage disease and for severe, refractory breathlessness, which is very distressing.

The overall evidence of effectiveness is limited. Still, the pharmacological treatment of breathlessness is in many cases the last option to achieve symptom relief. As it may also be associated with adverse effects,[6,11,17–22] it is particularly important to weigh benefit and harm carefully.

1. Opioids

(a) Consider regular low-dose opioids titrated against effect for patients with severe, refractory breathlessness in COPD, cancer, or ILD

Five systematic reviews described a benefit for opioids in general,[18–21,23] one stated no benefit compared to placebo or anxiolytics,[24] and one had inconclusive results.[25] The strongest evidence available supports the use of morphine.[18,20,22,26,27] The evidence for nebulized opioids is limited to insufficient.[18–20,22,28] Overall, systematic reviews underline the low quality of evidence and the limited number of studies.[18–26,28]

Nevertheless, international guidelines recommend opioids for breathlessness in patients with cancer, COPD, or ILD when non-pharmacological interventions are insufficient.[6,11–13,29–31] Opioids should be started with a low dose and titrated against effect.[6,11,31]

(b) Where possible, use modified release (slow release) formulation

In patients with controlled breathlessness, rapid-release opioids should be replaced by slow release opioids.[31] However, ongoing studies will provide more evidence soon.[32]

(c) Reduce dose and/or increase dosing interval for renal failure and consider alternatives such as fentanyl

In patients with renal insufficiency, the dose and type of opioid should be adjusted.[11,13,33] This should be considered when the glomerular filtration rate is <30ml/min with a risk of opioid accumulation.[13,33] ~~A recommended opioid for renal insufficiency is fentanyl.[11,13]~~

(d) Start laxatives for the prophylaxis and treatment of constipation if indicated

One of the most frequently reported side effects of opioids in systematic reviews is constipation.[17–19,22] Constipation persists in contrast to other side effects like nausea.[6] Therefore, guidelines recommend patients' and carers' education and prophylaxis for constipation, such as laxatives.[6,11,13]

(e) Consider anticipatory treatment for nausea/vomiting as a side effect

Further common side effects in systematic reviews are nausea[17–19,22] and vomiting.[17,18,22] Guidelines recommend prophylaxis for side effects, for example antiemetics, as needed.[6,11,13] Side effects and their prophylaxis should be considered especially in the initial phase.[13]

(f) Monitor for adverse effects such as respiratory failure or drug dependence and/or withdrawal symptoms

For low doses, systematic reviews found no evidence of clinically relevant respiratory depression,[17,19,21,25] but there have been associations with increased mortality and morbidity in large retrospective data set analyses in COPD elsewhere in the literature.[34,35] A large multi-centre trial of morphine in breathlessness (MABEL) that will help to provide robust evidence of the benefit and harms of morphine is currently underway.[32] Drug dependence and/or withdrawal symptoms can cause additional problems and be potentially life-threatening in patients not at the end of life. Older adults with multiple comorbidities are predisposed to opioid-related adverse pulmonary events, as this has been described elsewhere[36] and prescribers should additionally be vigilant to signs of drug dependence and/or withdrawal symptoms. Even in end-of-life care, risk and benefit need to be balanced carefully.

2. Benzodiazepines

(a) Consider benzodiazepines only if the predominant symptom is anxiety/panic associated with severe, refractory breathlessness

A systematic review on benzodiazepines for breathlessness found no evidence for an effective relief of breathlessness intensity.[37]Klicken oder tippen Sie hier, um Text einzugeben. Breathlessness is often associated with anxiety and panic and can be worsened by each other. The effectiveness of benzodiazepines in relieving anxiety and panic has been established elsewhere.[38] Therefore, only a selected patient group with the predominant symptom of anxiety/panic associated with severe breathlessness, which cannot be relieved by non-pharmacological interventions and after careful weighting between benefit and harm, should be considered for a trial of low dose benzodiazepines. To

state, there is an ongoing discussion between experts and in guidelines whether to use benzodiazepines at all in this situation.[39]

(b) Monitor adverse effects carefully such as sedation, increased tendency to fall, paradoxical effect, or addiction

As the evidence is limited and insufficient, it is paramount in the use of benzodiazepines to monitor potential adverse effects of benzodiazepines to do no harm. All experts and guidelines recommend the assessment of potential effects as sedation, falls (in particular in elderly), paradoxical effects, and the risk of addiction.[6,11]

3. Only in the last days of life (dying phase), consider the combination of opioids and benzodiazepines when the relief of severe, refractory breathlessness (and maybe anxiety) cannot be achieved otherwise

The simultaneous use of benzodiazepines and opioids increases the risk of adverse effects which cause harm and should be avoided. However, if severe breathlessness in the dying phase causes distress and cannot be alleviated by other means, clinical experience has shown that the combination of opioids and benzodiazepines may be effective. The simultaneous use is also recommended by an oncology guideline[13] and a COPD guideline.[31]

Practice Recommendations 'Do not'

1. Don't routinely use pharmacological treatment as first-line treatment unless the patient is in the last days of life

Due to the limited evidence of pharmacologic therapies, they should not be used as first-line therapy. Instead, as stated in "Do's", it should always be considered first whether non-pharmacological interventions are feasible and sufficient.

2. Don't routinely use doses of opioids >30mg oral morphine equivalent/24hrs in patients with COPD

Several guidelines recommend morphine doses less than 30mg/day because of higher doses of opioids are associated with an increased mortality.[6,11–13,31,40,41]

3. Don't routinely use benzodiazepines >1mg lorazepam equivalent/24 hrs and avoid long-term use unless there is clear evidence of individual patient benefit

Guidelines rarely recommend the use of benzodiazepines, because of an association between mortality and higher doses of benzodiazepines. If at all, only a low dose of benzodiazepines should be used by monitoring potential side effects carefully.[6,11,13,34,42,43]Klicken oder tippen Sie hier, um Text einzugeben.

4. Don't routinely use corticosteroids for the relief of chronic breathlessness unless there is clear evidence of individual patient benefit

One systematic review including two RCTs on beclomethasone for patients with COPD did not show a significant difference as compared to placebo.[44] One systematic review on cancer-related breathlessness found no clear difference compared to placebo.[45] For patients with ILD, the number of studies is also limited [23]. Another review described the strength of evidence as insufficient.[24]

Current guideline recommendations for corticosteroids for cancer-related breathlessness are limited.[6,11,13,31] Two guidelines give a weak recommendation for corticosteroids when breathlessness is caused for example by inflammation.[6,31] Overall, there is evidence of insufficient effect of corticosteroids or a lack of evidence.[23,24,44,45] Further, evidence of harm in idiopathic pulmonary fibrosis[46] and in cancer has been highlighted elsewhere in the literature.[47] For these reasons, corticosteroids are not recommended to reduce breathlessness. Note that this recommendation only addresses the symptomatic treatment of chronic breathlessness. However, corticosteroids can be indicated for the treatment of the underlying condition (e.g. COPD) following current guidelines.[30]

5. Antidepressants for the relief of breathlessness

There is new evidence from two large RCTs and one pilot RCT about the effectiveness of antidepressants for the relief of chronic breathlessness (all participants without a diagnosis of depression).[48] The recently published placebo-controlled RCT (European BETTER-B trial) evaluating mirtazapine in 225 patients with COPD/ILD and chronic breathlessness did not show any improvement of breathlessness but more adverse effects.[48] An RCT testing sertraline in 223 patients with life limiting disease and chronic breathlessness could also not find a statistical benefit over placebo for the relief of breathlessness.[49] The third RCT - a feasibility trial evaluating mirtazapine - was not designed to demonstrate effectiveness (see Supplement 3).[50]

Based on this new evidence, the use of antidepressants cannot be recommended for the relief of chronic breathlessness.

6. Don't routinely use pharmacological treatment for known breathlessness episodes with an onset of effect longer than the breathlessness episode lasts

A breathlessness episode is an acute form of breathlessness (syn. attack) and lasts on average only few minutes (75% less than 10min).[21,51,52] Therefore, drugs whose onset of action lasts longer than a usual episode should not be administered.[51,52]

'Don't know' if there is a benefit of

1. Opioids for the relief of chronic breathlessness in patients with CHF

While evidence underpinning the recommendation on opioids for the relief of chronic breathlessness in patients with COPD, cancer and ILD is of low quality, it is even more limited in patients with CHF as to formulate a recommendation. A current systematic review and meta-analysis on breathlessness in patients with advanced CHF found no significant benefit of opioids but significantly more adverse effects compared to placebo.[17] The authors suggest further research while considering the multidimensionality of breathlessness and a possible beneficial effect in selected responders. An ongoing trial might give more insight on the topic.[32]

Limitations

The literature search was based on a scoping review methodology, for which we developed pragmatic search strategies, considered predefined inclusion criteria for selection, but did not appraise the evidence quality. Despite having been conducted thoroughly, the review might not have yielded all the relevant evidence.

Summary

As only limited evidence for drug therapy is available, the first-line treatment option for the relief of chronic breathlessness is the use of non-pharmacological interventions. Opioids are the only drug with some but weak evidence and conflicting results in clinical trials. Therefore, opioids should be used with caution and by low-dose. The use of benzodiazepines should be avoided and considered only for selected patients, e.g. with the predominant symptom of anxiety/panic associate with severe breathlessness. Antidepressants and corticosteroids should not be used for the relief of breathlessness. There is a further need for clinical trials and a lack of evidence for the use of opioids in patients with CHF.

Acknowledgements

We thank the members of the BETTER-B consortium for their support and valuable comments during the development of the recommendations.

Author contributions

Literature data search, screening and analysis of the studies, reviews and guidelines were done by CW, AP, and StS. A first draft of the recommendations and the practice review were prepared by CW, StS, and AP. All authors discussed and revised the review until a consent was reached. Additionally, the recommendations were discussed in a consensus process within the BETTER-B-Consortium.

Funding

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 825319. The European Commission is not responsible for any use that may be made of the information in contains

Declaration of conflicts of interests

All authors declare no conflicts of interests.

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BETTER-B (BETter TreatmEnts for Refractory Breathlessness in Palliative and End of Life Care) is an international, multicentre study, at the centre of which is a randomised controlled pragmatic trial of mirtazapine to alleviate breathlessness in palliative and end of life care (EudraCT 2019-002001-21), led by King's College London, Cicely Saunders Institute, Department of Palliative Care, Policy & Rehabilitation, UK. The views expressed in this publication are those of the authors and not necessarily those of the European Commission.

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Supplemental material

Supplemental material for this article is available online.

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