Non-opioid medications for the relief of chronic breathlessness: current evidence

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Non-opioid medications for the relief of chronic breathlessness: current evidence

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Abstract

Introduction: To evaluate systematically randomised clinical trials investigating non-opioid medications for the management and treatment of chronic breathlessness.

Areas Covered: The evidence for the role of benzodiazepines, anxiolytics, selective serotonin re-uptake inhibitors (SSRIs), tricyclic antidepressants, antihistamines, cannabinoids, nebulized furosemide and herbal-based treatments were critically reviewed. Search of the Clinical Trials Registry (Clinicaltrial.gov) identified ongoing studies expected to generate new data in the near future in several classes of non-opioid medications for their net effect on chronic breathlessness.

Expert Commentary: Morphine still has the best levels of evidence for the symptomatic treatment of chronic breathlessness. Non-opioid treatments for chronic breathlessness are less studied than morphine and morphine-related medications although evidence is emerging in relation to some options. Currently, there is insufficient evidence to recommend non-opioids in the routine treatment of chronic breathlessness. There is a need to find agents, new as well as re-purposed, that can be used as alternative therapies to opioids for chronic breathlessness for people who are unable to tolerate morphine.

Key words: breathlessness; dyspnoea; anxiolytic; anti-depressant; nebulized furosemide
1.0 INTRODUCTION

Chronic breathlessness is a core issue for all physician and other health professionals involved in the care of people with a variety of advanced medical conditions. Despite optimal treatment of the underlying pathologies, the multidimensional experience of distressing chronic breathlessness remains a major problem for patients, their family caregivers and clinicians, often leaving all feeling helpless.

Neuroimaging studies have shown the central pathways involved in response to breathlessness include several limbic, paralimbic and cerebellar loci. This, along with a growing understanding of the role of endogenous opioids and serotonin in breathing, and the relationship between breathlessness and anxiety and depression, has led to calls to find ways to modulate central neural activity in relation to breathlessness and thus alleviate the unpleasantness, intensity, and emotional and functional responses to breathlessness. A range of potential drug intervention candidates aiming to modulate central perception have been investigated. This systematic review summarises the evidence so far and discusses the implications for current clinical practice, and for future research.

2.0 IDENTIFICATION OF LITERATURE

To identify potential studies we searched MEDLINE, EMBASE, Google Scholar for randomised controlled trials investigating the role of potential non-opioid medications for the relief of chronic breathlessness due to medical conditions. We included studies where chronic breathlessness due to medical conditions was measured as a primary or secondary outcome. Clinical trials and relevant retrospective and prospective observational studies (especially if trials were few or lacking) exploring the role of a specific drug-classes were included. The reference lists of studies identified and relevant reviews were hand-searched. We also searched registers of clinical trials for further ongoing or unpublished studies, up to November 2016.

List of terms and words used for the systematic search and review of published clinical trials: “dyspnea”, “dyspnoea”, “breathlessness”, “symptom”, “drug”, “agent”, “benzodiazepines”, “anxiolytic”, “antihistamines”, “SSRI”, “selective serotonin reuptake inhibitor”, “tricyclic antidepressant”, “anti-histamine”, “nebulized furosemide”, “inhaled furosemide”, “herbs”, “herbal”, “cannabis”, “tetrahydrocannabinol”. Steroids were not included as they most likely mediate any effect on breathlessness indirectly through their anti-inflammatory actions on the underlying disease process rather than directly modifying the perception (e.g. asthma, peritumour oedema in lymphangitis carcinomatosis). Antihistamines were included because they also have central sedative effects.

One researcher (CB) screened titles, abstracts, retrieved papers and extracted data. Uncertainty regarding inclusion was resolved by discussion with MJ.

3.0 FINDINGS

The findings are presented by drug class.
3.1 Anxiolytics

3.1.1. Benzodiazepines

Anxiolytics, such as benzodiazepines, are commonly used to help to reduce chronic breathlessness in palliative care settings. The need for robust placebo-controlled safety data regarding benzodiazepines is illustrated by recent observational studies. A population registry-based, longitudinal, consecutive cohort study on 2249 people with severe COPD on long term oxygen found that benzodiazepines and low dose oral morphine ($\geq 30$mg morphine equivalent daily dose) were not associated with increased hospital admission, but benzodiazepines (but not low dose morphine) were associated with increased mortality in a dose-related manner. A risk of increased respiratory adverse events due to use of benzodiazepines in people with COPD was also highlighted by Vozoris et al in a large cohort study. In benzodiazepine-naïve people with COPD a new prescription of benzodiazepines was linked to an increased rate of outpatient respiratory exacerbations ($RR \ 1.45 \ CI \ 1.36\sim1.54$) compared to non-users.

A pilot phase I open label trial evaluated the role of oral clonazepam 0.5 nocte and 10 mg oral sustained release morphine, administered for at least 4 days, in 11 people with COPD and chronic breathlessness (modified Medical Research Council dyspnoea scale [mMRC] $\geq 2$). Despite the study’s limitations, a positive effect of clonazepam in reducing breathlessness by 15% over baseline was found, indicating the need for further study. A retrospective analysis of 115 clinical records in a population of people with cancer, heart failure or COPD suggested that patients receiving opioids and benzodiazepines showed greater improvement of breathlessness compared to those receiving only opioids or benzodiazepines. Midazolam was also used in a palliative sedation protocol in 4 people in the last hours or days of life with cancer and severe breathlessness, and was reported to be effective. The safety of lorazepam 1 mg sublingually in addition to opioids was evaluated in a prospective non-randomised study of 26 patients admitted to a palliative care unit with chronic breathlessness and anxiety. Lorazepam combined with opioids appeared to be safe and effective in relieving breathlessness and anxiety in the palliative care setting since no clinically important variations of $SpO_2$ and $pCO_2$ were recorded. Breathlessness and anxiety were recorded and monitored with a 0-10 numeric rating scale (NRS) however; sedated patients might not have been able to distinguish between the two sensations. This might explain the similar scores and the very strong relationship observed between chronic breathlessness and anxiety ($r= 0.952, p< 0.0001$).

3.1.1.1. Randomised controlled trials

A recently updated Cochrane review of a range of benzodiazepines (diazepam, midazolam, alprazolam, lorazepam) showed no evidence of a net benefit on chronic breathlessness in people with cancer or COPD when compared to placebo. The review concluded that any use of benzodiazepines for chronic breathlessness should be as a second or third-line treatment within a carefully monitored individual therapeutic trial. Route of administration was not significant in sensitivity analysis. The pressing need is for adequately powered, randomised controlled trials in order to inform clinicians in everyday practice rather than further phase II studies or case series.

3.1.2 Buspirone
Buspirone, an azapirone which does not suppress respiration used in the management of generalized anxiety disorders, has been suggested as a potential modulator of chronic breathlessness. Small, underpowered trials have given mixed results,\textsuperscript{21,22} however, a recent phase III clinical trial in people with cancer and chronic breathlessness showed no improvement in breathlessness.\textsuperscript{23} This large study showed no sign of benefit and whether it should be repeated in patients other than those with cancer remains open to discussion.

3.1.3 Ondansetron

Ondansetron is a serotonin antagonist, commonly used to treat chemotherapy-induced emesis. It is also considered to have a possible anxiolytic and anti-psychotic effect.\textsuperscript{24,25,26} Exploratory work investigated its potential role as a modulator of chronic breathlessness working on the insular cortex in a small RCT (n=10), but showed no benefit in healthy volunteers with experimentally induced acute breathlessness.\textsuperscript{27} A study of inhaled ondansetron (8 mg) compared to inhaled 0.9% saline in healthy subjects in whom acute breathlessness was induced by thoracic constriction and exercise [NCT01851993] is ongoing. It is not known how such findings will apply to the context chronic breathlessness.

3.2 Antidepressants

3.2.1 The epidemiology of chronic breathlessness and depression

Antidepressants such as selective serotonin re-uptake inhibitors (SSRIs) and tricyclic antidepressants have been studied for their potential role in reducing chronic breathlessness.\textsuperscript{28} A pathophysiological link between respiratory and psychiatric symptoms could be found at the level of serotonergic system and its effect on the modulation of central respiratory control and sensitivity to carbon dioxide. A cross sectional study of 836 people with COPD estimated the prevalence of depression and related symptoms.\textsuperscript{29} About three quarters of this large unselected population of COPD patients had depression; this was moderate or severe in half (51.5%). Depression was associated with a poorer quality of life (QoL), increased rates of exacerbations and higher prevalence of comorbidities. Breathlessness prevalence was associated significantly in people with COPD and depression. Another cross-sectional observational study of 54 people with COPD explored the relationship between anxiety, depression, breathlessness and thoraco-abdominal mechanics at rest and/or during exercise. Anxiety and depression were associated with poorer clinical disease control and depressive symptoms were associated with breathlessness, independent of breathing pattern and thoraco-abdominal mechanics.\textsuperscript{30}

3.2.2 Randomised controlled trials

Exploratory studies of people with COPD are limited by the small sample sizes and underlying methodologies used.\textsuperscript{19,31-36} These provide preliminary support to further explore a role for these drugs in reducing anxiety and chronic breathlessness, and improving quality of life. However, a Cochrane Review in 2011 failed to demonstrate conclusive evidence for SSRI and tricyclic antidepressants in managing breathlessness, despite improvement in anxiety, quality of life and exercise tolerance with paroxetine 20 mg/daily.\textsuperscript{37} A randomised trial of 138 patients with COPD and major depression compared a Personal Intervention (PID-COPD) against usual care over 28 weeks; findings showed that PID-COPD led to an interacting spiral of improvement, improved adherence with antidepressant treatment and COPD rehabilitation, and reduced breathlessness-related disability. However, in this complex intervention there
were different factors and drugs used and evaluation of particular sub-classes of antidepressants was not possible.\textsuperscript{38} An RCT of people with COPD and depression found that those allocated to fluoxetine 25 mg / daily in addition to usual care compared with usual care only had improvement in breathlessness scale scores, oxygenation and spirometry.\textsuperscript{39}

Dale et al. (2012) enrolled 36 people with cancer in a cross over, double blind randomised trial to evaluate mirtazapine (15mg vs 30 mg), showing improvement of many cancer related symptoms and QoL.\textsuperscript{40} A phase II trial is ongoing to test the feasibility of a phase III trial to evaluate mirtazapine for the management of chronic breathlessness due to a variety of optimally treated medical conditions.[Eudract number 2015-004064-11]

Phase III RCTs are required to give definitive evidence of these agents for the treatment of breathlessness; one is due to report early 2017 (ACTRN12610000464066; sertraline for chronic breathlessness).\textsuperscript{41} A safety trial in people with COPD undergoing pulmonary rehabilitation is underway ([NCT02813447]; primary outcomes of breathlessness scores, quality of life and exercise tolerance measures will be primary outcomes.

3.3 Antihistamines

Antihistamine agents (anti-H1) have been investigated alone or in association with benzodiazepines or morphine to reduce breathlessness. These drugs have anti-muscarinic and anti-serotonergic activity leading to sedative and antipsychotics effects.\textsuperscript{42} Promethazine has been investigated in different settings to evaluate a potential role in breathlessness management and as an opioid-sparing treatment.

Six healthy volunteers took promethazine 25 mg orally before a treadmill test and reported reduced effort-induced acute breathlessness (VAS) although this did not reach statistical significance.\textsuperscript{43} The finding was not confirmed in another study of 12 healthy subjects.\textsuperscript{44} In this study, half also received chlorpromazine; these participants had a statistically significant improvement in acute breathlessness scores (mean relative reduction 19.3%), with no evidence of respiratory depression. The application of these findings to the clinical setting of chronic breathlessness has not been studied at this time.

An evaluation of the effect of 125mg promethazine daily for two weeks in 15 men with COPD ("pink puffer" phenotype) showed a reduction in breathlessness scores and improved exercise tolerance.\textsuperscript{45} However, promethazine 100 mg daily given to 11 people with COPD showed no improvement in breathlessness at 1 month.\textsuperscript{46} An evaluation of 25 mg promethazine together with morphine 30 mg administered before exercise in 7 men with COPD gave improved exercise tolerance and increased maximum minute ventilation, but showed no differences in perceived breathlessness (Borg scale).\textsuperscript{47} These findings cannot be applied to clinical practice at this time.

3.4 Cannabinoids

Cannabis and cannabis-related molecules have been investigated to evaluate their potential role in the treatment of several symptoms in a wide sub-set of patients. A recent meta-analysis, conducted according to Cochrane criteria, highlighted both the potential benefit and appreciable risks of these drugs.\textsuperscript{48} Cannabinoids have been studied by Pickering et al. as a potential treatment for breathlessness in a small (9}
patients, 4 with moderate COPD) RCT comparing the effect of cannabis-based medicinal extract with placebo in reducing acutely induced breathlessness. Results showed no changes on VAS measurements although COPD patients used fewer "breathlessness" descriptors. Participants reported adverse events (intoxication and reversible cardiac dysrhythmias). Therefore current evidence does not support the use of acutely administered cannabinoids for breathlessness.

3.5 Nebulized furosemide

Animal models suggest a potential role for furosemide in changing local chloride ion channels and its negative effect on c-fibers receptor and vagal irritant receptors, and an associated positive effect on alveolar stretch receptors. Nebulised inhaled furosemide (NIF) has been tested in acute breathlessness induced in healthy volunteers and in people with acute asthma, COPD, heart failure and lung cancer.

3.5.1 NIF in experimental settings

Three studies tested NIF 40 mg compared to 0.9% saline in 32 subjects (respectively n=12, n=10, n=10) evaluating its role in reducing breathlessness and air hunger during experimental conditions (loaded breathing test, breath holding, CO₂ chemosensitivity measured by the steady-state and rebreathing methods, hypercapnia during constrained ventilation) in double blind randomised cross over trials. Findings showed a reduction in breathlessness which was not correlated with the ventilator drive of CO₂. NIF 40 mg, 80 mg or normal saline in 9 healthy subjects found no benefit from NIF in alleviating respiratory effort during flow limited exercise.

3.5.2 NIF and COPD

NIF 40 mg was compared to 0.9% saline in two studies in 19 people with COPD respectively undergoing exercise tests (incremental exercise, symptom limited exercise) to induce breathlessness. Both trials showed a reduction in breathlessness intensity, increased exercise endurance and optimisation of lung volumes, with an improvement in SpO₂ levels rather than a diuretic effect. NIF 40 mg compared to 0.9% saline in 100 people with exacerbations of COPD admitted to an emergency department showed that those allocated to NIF had a statistically significant improvement in Borg scores, spirometry, blood gases, heart and respiratory rate, and blood pressure. All subjects also inhaled salbutamol and ipratropium, and received intravenous hydrocortisone. These data suggest that a trial of NIF 40 mg to reduce chronic breathlessness in COPD exacerbations is safe, while further work is needed to evaluate its role in relieving chronic breathlessness. Cardiovascular co-morbidities are frequent in people with moderate or severe COPD. None of these studies noted this comorbidity so work is needed to evaluate the effect of NIF on chronic breathlessness as a result of cardiac failure. Recently NIF was compared to normal saline in people with stable advanced heart failure (32 patients) undergoing right heart catheterisation. No difference were observed in haemodynamic parameters in the one hour after administration of the drug, but a diuretic effect was seen in those allocated to NIF. Breathlessness was not measured in this study. Further research is warranted.

3.5.3 NIF and cancer
NIF has been tested to reduce chronic breathlessness in people with lung cancer. Studies are small and have found mixed results. 60 61 62 63

All these studies have used nebulised saline as the control arm and used either jet or ultra-sonic nebulizers. It is important to note that nebulised saline, administered via an efficient nebulizer, improved breathlessness scores and sputum clearance in people with COPD and therefore may have a role in its own right in the relief of breathlessness, and makes the interpretation of studies of nebulised agents more challenging. 64

Currently two clinical trials of nebulised furosemide to reduce chronic breathlessness are registered as open. NCT01851980 will investigate the role of NIF on Physical Activity-Related Breathlessness in a human model of exercise-induced breathlessness (primary outcome: intensity of breathlessness on a Borg 0-10 scale); and NCT02524054 aims to evaluate NIF in patients with refractory breathlessness (primary outcome: intensity of breathlessness on a VAS). Results are expected during 2017.

3.6 Herbal based treatments

Herbal based treatments such as Bu-Fei Jian-Pi granules, Bu-Fei Yi-Shen granules and Yi-Qi Zi-Shen granules in addition to standard GOLD guideline COPD therapy have shown reduction in breathlessness in an open-label RCT of 352 people with COPD. 66 Further, a secondary sub-set analysis on 136 patients older than 65 years old, saw the same result. 65 These different kinds of granules have been administered to specific patient clusters, according to the traditional Chinese medicine. Further research based on designed placebo controlled RCT in breathlessness patients, alongside systematic documentation of toxicities is therefore advised.

4.0 CONCLUSIONS

Extended release morphine remains the most studied symptomatic treatment for chronic breathlessness. There is an urgent continuing need to explore other therapeutic interventions. Such studies are, in part, based on the emerging knowledge of the central pathways and receptors involved in the perception and modulation of the perception of chronic breathlessness.

This review summarises the current evidence for currently available agents with regard to potential repurposing for the management of breathlessness. None have more than preliminary evidence to support their use and some have evidence to show they have no role. Further work is required for those with potential. It is not possible currently to make recommendations with regard to which drug for which person. There is also a need to identify new agents specifically developed to interact with the perception of breathlessness safely.

5.0 EXPERT COMMENTARY

Chronic breathlessness due to medical conditions has a serious impact on the daily experience of those who live with it, their family and friends and the health and social care professionals. 67 68 It is more strongly associated with survival than surrogate markers of lung function, 69 and people with chronic breathlessness
are more likely to have poor quality of life,\textsuperscript{70} anxiety and depression,\textsuperscript{71} and increased health service utilisation especially emergency services.\textsuperscript{72} Breathlessness, in a traditional medical model, views the symptom largely as a diagnostic signpost, with the focus of management thereafter being interventions for the causative medical condition. However, despite optimum disease-directed treatment, breathlessness will persist for many, especially as the disease advances. There are evidence-based treatments for chronic breathlessness itself, particularly based on non-pharmacological interventions which remain the bedrock of breathlessness management. However, they are not implemented systematically into clinical practice partly due to lack of clinician education and partly due to lack of resources. Further, patients may persist with troublesome chronic breathlessness despite such measures, in which case, pharmacological approaches may be of use. Recourse to pharmacological measures may be needed sooner in people with a rapid decline, than those with a more stable trajectory. The evidence base for pharmacological interventions is growing, but is strongest for oral low-dose morphine. However, not all patients will tolerate morphine and other pharmacological approaches are needed.

There are a number of published clinical trials of mainly preliminary evaluation of a range of medications which have a biologically plausible rationale for re-purposing for breathlessness management. These include anxiolytics, antidepressants, antihistamines, cannabinoids and nebulised furosemide. Only one adequately powered trial of an anxiolytic has been reported so far (buspirone vs placebo in people with breathlessness due to cancer) which demonstrated no benefit. This trial, however, shows the importance of trials which recruit to their \textit{a priori} sample size as previous phase II work had indicated benefit. A phase III trial for sertraline is due to report in 2017. However, much of the other work has failed to show promise, or has been inconclusive. The exception perhaps is nebulised medication such as furosemide and normal saline where further study seems to be warranted. The ultimate goal in this field is to be able to offer patients tailored pharmacological interventions to benefit chronic breathlessness thereby improving functional ability, quality of life and levels of independence.

Future work requires well designed trials with adequate power to test the effectiveness of both re-purposed drugs and also newly developed compounds. Therefore greater understanding of the pathophysiological pathways of the genesis and perception of chronic breathlessness itself is needed to inform potential targets for new interventions. A better understanding of whether benefits seen for breathlessness in one medical condition are replicated in another. For example, is the improvement in breathlessness with nebulised normal saline in people with COPD mediated through improved mucous clearance and if so, does this mean that the benefit would not be seen in patients with interstitial lung fibrosis? Another challenge is the need to understand how health service provision for such patients should be best provided in order to implement interventions directed at both the underlying disease and the ongoing symptom in an integrated manner.

Current developing areas of research include work to understand the pathways of central perception of chronic breathlessness, the effectiveness and implementation of complex interventions for breathlessness in different settings, and systematic testing of medications to improve this previously neglected symptom.
6.0 FIVE-YEAR VIEW

With regard to non-opioid medication for the management of chronic breathlessness, we anticipate that in five years, research with selective serotonin reuptake inhibitors (SSRI) and serotonin and noradrenaline inhibitors (SNRI) will be defined for their net effect on chronic breathlessness. We should have a clearer understanding of the role of nebulised furosemide. We hope that multi-disciplinary breathlessness assessment and management as a specific focus alongside ongoing optimisation of the underlying cause(s) will become a routine part of clinical practice.

7.0 KEY ISSUES

- Morphine has the best levels of evidence for the symptomatic treatment of chronic breathlessness.
- Non-opioid treatments for chronic breathlessness are less studied than morphine and morphine-related medications although evidence is emerging in relation to some options. In particular there is evidence that buspirone is ineffective in people with cancer and nebulized normal saline is helpful in people with COPD.
- Currently, there is insufficient evidence to recommend non-opioids in the routine treatment of chronic breathlessness. Results from a phase III trial of sertraline vs placebo in people with chronic breathlessness due to a variety of causes will report in 2017.
- There is a need to find agents, new as well as re-purposed, that can be used as alternative therapies to opioids for chronic breathlessness for people who are unable to tolerate morphine.

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Declaration of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.
8.0 REFERENCES

Papers of special note have been annotated as:
* Of interest
** Of considerable interest

1 Bausewein, Currow DC, Johnson MJ Palliative care in Respiratory Medicine ERS Monograph 2016 doi: 10.1183/2312508X.erm7316

** This brings together current knowledge about palliative care in respiratory medicine and includes epidemiology through to patient and carer experience to symptom management. A summary of this paper appears in the chapter on breathlessness management.


* This paper provides a fascinating rationale for the role of serotonin in breathlessness


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14 Ekström MP, Bornefalk-Hermansson A, Abernethy AP, Currow DC Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study BMJ 2014; 348:g445

** This registry based study of people with advanced COPD showed no association with hospital admission or death in those taking 30mg per day morphine or less.


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19 Clemens KE, Klaschik E Dyspnoea associated with anxiety—symptomatic therapy with opioids in combination with lorazepam and its effect on ventilation in palliative care patients Support Care Cancer 2011; 19:2027–2033


** This review presents the lack of evidence for benzodiazepines for the benefit of breathlessness


** Phase III trial shows no benefit of buspirone over placebo showing the need for placebo controlled trials of repurposed drugs.


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31 Gordon GH, Michielis TM, Mahutte CK, Light RW Effect of Desipramine on Control of Ventilation and Depression Scores in Patients With Severe Chronic Obstructive Pulmonary Disease Psychiatry Research 1985: 15, 25-32


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Table 1: Benzodiazepines for breathlessness. Reproduced with permission of the European Respiratory Society ©

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Study design</th>
<th>Drug tested</th>
<th>Patients enrolled</th>
<th>Breathlessness measure</th>
<th>Benefit perceived on acute-induced Breathlessness (AIB) Vs Chronic Breathlessness (CB)</th>
<th>Statistically significant benefit breathlessness</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simon 2016 20</td>
<td>Cochrane systematic review</td>
<td>alprazolam, diazepam, midazolam, lorazepam, clorazepate, temazepam</td>
<td>COPD Cancer</td>
<td>VAS Breathlessness grade scale Borg scale Multidimensional scales (SGRQ, CRQ)</td>
<td>CB</td>
<td>No</td>
<td>Simon 2016 20</td>
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<tr>
<td>Clemens 2011 19</td>
<td>Prospective, non randomised</td>
<td>Oral lorazepam 1 mg and morphine as needed</td>
<td>26 patients admitted to a palliative care unit</td>
<td>Numeric scale (0-10)</td>
<td>CB</td>
<td>No</td>
<td>Safety* of co-administration</td>
</tr>
<tr>
<td>Allcroft 2013 16</td>
<td>Open label trial</td>
<td>Oral clonazepam 0.5 mg nocte and morphine extended release 10 mg</td>
<td>11 COPD with mMRC&gt; 2</td>
<td>CB</td>
<td>5 patients reported benefit</td>
<td>Safety* of co-administration</td>
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<tr>
<td>Hardy 2016 13</td>
<td>Randomised, double blind, cross over trial</td>
<td>Intransal midazolam</td>
<td>62 between cancer, chronic heart failure, COPD</td>
<td>0-10 breathlessness score, HADS, Cancer dyspnoea scale</td>
<td>CB</td>
<td></td>
<td></td>
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</tbody>
</table>

* safety was defined as effect of benzodiazepines on breathing, ventilation and gas exchanges. COPD – chronic obstructive pulmonary disease; VAS – Visual Analogic Scale; HADS - Hospital Anxiety and Depression Scale; RCT – Randomised clinical trial; mMRC – modified Medical Research Council breathlessness scale; BDZ – benzodiazepines; SGRQ - St. George’s Respiratory Questionnaire, CRQ - Chronic Respiratory Disease Questionnaire
Table 2: Buspirone for breathlessness

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Type of study</th>
<th>Drug tested</th>
<th>Patients enrolled</th>
<th>Breathlessness measure</th>
<th>Statistically significant benefit breathlessness</th>
<th>Benefit perceived on acute-induced Breathlessness (AIB) Vs Chronic Breathlessness (CB)</th>
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<td>Argyropoulou 1993</td>
<td>RCT</td>
<td>20 mg Buspirone</td>
<td>16 COPD</td>
<td>BORG</td>
<td>No</td>
<td>AIB</td>
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<tr>
<td>Singh, 1993</td>
<td>RCT</td>
<td>30-60 mg Buspirone</td>
<td>11 COPD</td>
<td>BORG</td>
<td>No</td>
<td>AIB and CB</td>
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<tr>
<td>Peoples, 2015</td>
<td>RCT</td>
<td>10-20 mg Buspirone</td>
<td>432 Cancer</td>
<td>OCD, STAI-S</td>
<td>No</td>
<td>CB</td>
</tr>
</tbody>
</table>

COPD – Chronic Obstructive pulmonary disease; OCD – Oxygen Cost diagram; STAI-S State-Trait Anxiety Inventory
### Table 3: Antidepressants for breathlessness

<table>
<thead>
<tr>
<th>Antidepressants, SSRI</th>
<th>First Author, Year</th>
<th>Type of study</th>
<th>Drug tested</th>
<th>Patients enrolled</th>
<th>Breathlessness measure</th>
<th>Statistically significant benefit breathlessness</th>
<th>Notes</th>
<th>Benefit perceived on acute-induced Breathlessness (AIB) vs Chronic Breathlessness (CB)</th>
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<tr>
<td>Gordon, 1985</td>
<td>RCT</td>
<td>25-100 mg despiramine</td>
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<td>n.a.</td>
<td>n.c.</td>
<td>Poor compliance, adverse reactions</td>
<td>CB</td>
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</tr>
<tr>
<td>Light, 1986</td>
<td>RCT</td>
<td>105-128 mg doxepine</td>
<td>12 COPD</td>
<td>n.a.</td>
<td>n.c.</td>
<td>Improvement in 12MWT</td>
<td>AIB</td>
<td></td>
</tr>
<tr>
<td>Borson, 1992</td>
<td>RCT</td>
<td>nortriptyline</td>
<td>30 COPD</td>
<td>n.a.</td>
<td>n.c.</td>
<td>Improvement in “respiratory symptoms”</td>
<td>CB</td>
<td></td>
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<tr>
<td>Grove, 1995</td>
<td>RCT</td>
<td>60-90 mg mianserin</td>
<td>12 COPD</td>
<td>n.a.</td>
<td>No</td>
<td>The study was designed to identify difference from oral corticosteroids</td>
<td>AIB and CB</td>
<td></td>
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<tr>
<td>Dale 2002</td>
<td>Open label, cross-over RT</td>
<td>15-30 mg mirtazapine</td>
<td>36 cancer</td>
<td>n.a.</td>
<td>n.c.</td>
<td>Improvement of cancer – related</td>
<td>CB</td>
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</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Intervention</td>
<td>Sample</td>
<td>Measure</td>
<td>Efficacy</td>
<td>Symptoms</td>
<td>Notes</td>
<td></td>
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<td>-----------------------</td>
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<td>----------------------------</td>
<td></td>
</tr>
<tr>
<td>LaCasse 2004</td>
<td>RCT</td>
<td>5-20 mg paroxetine</td>
<td>23 COPD</td>
<td>CRQ</td>
<td>No</td>
<td>Dyspnea not improved</td>
<td>CB</td>
<td></td>
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<tr>
<td>Eiser 2005</td>
<td>RCT</td>
<td>20 mg paroxetine</td>
<td>28</td>
<td>SGRQ</td>
<td>Yes</td>
<td>Reduce anxiety, improved effort tolerance and QoL, but only when administered for 3 months</td>
<td>CB</td>
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<tr>
<td>Alexopoulous 2014</td>
<td>RCT</td>
<td>Any antidepressant</td>
<td>138 COPD</td>
<td>DRDQ</td>
<td>Yes</td>
<td>-</td>
<td>CB</td>
<td></td>
</tr>
<tr>
<td>Momtaz 2015</td>
<td>RCT</td>
<td>20 mg fluoxetine</td>
<td>50 COPD</td>
<td>BORG</td>
<td>Yes</td>
<td>-</td>
<td>CB</td>
<td></td>
</tr>
</tbody>
</table>

COPD – chronic obstructive pulmonary disease; n.c. – not conclusive; n.a. – not available; QoL - Quality of Life; CRQ - Chronic respiratory questionnaire; SGRQ - St. George Respiratory questionnaire; DRDQ - Dyspnea related disability questionnaire
Table 4: antihistamines for breathlessness

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Type of study</th>
<th>Drug tested</th>
<th>Patients enrolled</th>
<th>Breathlessness measure</th>
<th>Statistically significant benefit breathlessness</th>
<th>Benefit perceived on acute-induced Breathlessness (AIB) Vs Chronic Breathlessness (CB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stark 1981</td>
<td>RCT</td>
<td>promethazine</td>
<td>6 healthy</td>
<td>VAS</td>
<td>Yes</td>
<td>AIB</td>
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<tr>
<td>Woodcock 1981</td>
<td>RCT</td>
<td>promethazine</td>
<td>15 COPD</td>
<td>Likert scale</td>
<td>Yes</td>
<td>AIB</td>
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<tr>
<td>O’Neill 1985</td>
<td>RCT</td>
<td>promethazine, chlorpromazine</td>
<td>12 healthy, 6 healthy</td>
<td>VAS, VAS</td>
<td>No, Yes</td>
<td>AIB</td>
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<tr>
<td>Rice 1987</td>
<td>RCT</td>
<td>promethazine</td>
<td>11 COPD</td>
<td>Subjective dyspnoea rating</td>
<td>No</td>
<td>AIB, CB</td>
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<tr>
<td>Light 1996</td>
<td>RCT</td>
<td>promethazine and morphine</td>
<td>7 COPD</td>
<td>BORG</td>
<td>No</td>
<td>AIB</td>
</tr>
</tbody>
</table>

COPD – Chronic Obstructive pulmonary disease; VAS – Visual Analogic Scale
<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Type of study</th>
<th>Drug tested</th>
<th>Patients enrolled</th>
<th>Breathlessness measure</th>
<th>Statistically significant benefit breathlessness</th>
<th>Benefit perceived on acute-induced Breathlessness (AIB) Vs Chronic Breathlessness (CB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nishino 2000</td>
<td>RCT crossover</td>
<td>NIF 40 mg</td>
<td>12 healthy</td>
<td>VAS</td>
<td>Yes</td>
<td>AIB</td>
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<tr>
<td>Minowa 2002</td>
<td>RCT</td>
<td>NIF 40 mg</td>
<td>10 healthy</td>
<td>VAS</td>
<td>Yes</td>
<td>AIB</td>
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<tr>
<td>Stone 2002</td>
<td>RCT crossover</td>
<td>NIF 20 mg</td>
<td>7 lung cancer terminal</td>
<td>VAS</td>
<td>No</td>
<td>CB</td>
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<tr>
<td>Ong 2004</td>
<td>RCT crossover</td>
<td>NIF 40 mg</td>
<td>19 COPD</td>
<td>VAS</td>
<td>Yes</td>
<td>AIB</td>
</tr>
<tr>
<td>Moosavi 2007</td>
<td>RCT crossover</td>
<td>NIF 40 mg</td>
<td>10 healthy</td>
<td>Effect on reduction of air hunger</td>
<td>Yes</td>
<td>AIB</td>
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<tr>
<td>Laveneziana 2008</td>
<td>RCT</td>
<td>NIF 40-80 mg</td>
<td>9 healthy</td>
<td>BORG</td>
<td>No</td>
<td>AIB</td>
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<tr>
<td>Jensen 2008</td>
<td>RCT crossover</td>
<td>NIF 40 mg</td>
<td>20 COPD</td>
<td>BORG</td>
<td>Yes</td>
<td>AIB</td>
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<td>Wilcock 2008</td>
<td>RCT</td>
<td>NIF 40 mg</td>
<td>15 cancer</td>
<td>BORG</td>
<td>No</td>
<td>AIB</td>
</tr>
<tr>
<td>Sheikh Motahar Vahedi 2013</td>
<td>RCT</td>
<td>NIF 40 mg</td>
<td>100 COPD during exacerbation</td>
<td>VAS</td>
<td>Yes</td>
<td>CB</td>
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</tbody>
</table>