

Progress in Palliative Care

What's Trending in Breathlessness Research? Proceedings of the 8th Annual Meeting of the Breathlessness Research Interest Group.

--Manuscript Draft--

Manuscript Number:	PPC252R1
Full Title:	What's Trending in Breathlessness Research? Proceedings of the 8th Annual Meeting of the Breathlessness Research Interest Group.
Article Type:	Discussion/Opinion paper
Keywords:	Breathlessness; Dyspnoea; Shortness of breath; Neuroimaging; Non-pharmacological Intervention; Carers; Stress
Corresponding Author:	Chloe Antoinette Chin Cambridge University Hospitals NHS Foundation Trust Cambridge, Cambridgeshire UNITED KINGDOM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Cambridge University Hospitals NHS Foundation Trust
Corresponding Author's Secondary Institution:	
First Author:	Chloe Antoinette Chin
First Author Secondary Information:	
Order of Authors:	Chloe Antoinette Chin
	Hanne Holt Butcher
	Anna Spathis
	Richella Ryan
	Miriam Johnson
	Kyle Pattinson
	David Currow
	Robert Banzett
	Janelle Yorke
	Helen Clayson
	Jane Macnaughton
	Clarissa Penfold
	Morag Farquhar
	Sara Booth
Order of Authors Secondary Information:	
Abstract:	<p>Breathlessness remains a challenging symptom, common to a multitude of malignant and non-malignant diseases, for which there are limited effective therapies once disease control is optimised. The American Thoracic Society (ATS) statement on dyspnoea reports that:</p> <ul style="list-style-type: none"> i)Progress in dyspnoea management has not matched progress in elucidating underlying mechanisms; ii)There is a critical need for interdisciplinary translational research to connect dyspnoea mechanisms with treatments; iii)There is a need to validate dyspnoea measures as patient-reported outcomes for clinical trials. <p>Research into the many dimensions of breathlessness and its significance to patients</p>

	<p>and their carers has increased in recent years. This meeting is convened yearly to bring together researchers across various disciplines including respiratory medicine, anaesthetics, medical humanities, engineering and palliative care, to further understanding of the symptom, discuss new techniques and advances in research, and pave the way forward for future studies and interventions.</p> <p>The presentations generated much vibrant discussion amongst the multidisciplinary attendees and highlighted areas where care for breathless patients could be improved. This is a positive time for breathlessness research, with several ATS research priorities being addressed and it is clear that further studies and ensuing interventions are on the horizon.</p>
--	---

What's Trending in Breathlessness Research?

Proceedings from the 8th Annual Meeting of the Breathlessness Research Interest Group

7th November 2014

Institute of Public Health, University of Cambridge

Organised by the Cambridge Breathlessness Research Group, Drs Sara Booth & Morag Farquhar.

Authors: CA Chin¹, H Holt Butcher², A Spathis¹, R Ryan¹, M Johnson³, K Pattinson⁴, D Currow⁵, R Banzett⁶, J Yorke⁷, H Clayson⁸, J Macnaughton⁹, C Penfold², M Farquhar², S Booth¹

¹Department of Palliative Medicine, Addenbrooke's Hospital, Cambridge, UK

²Primary Care Unit, Department of Public Health & Primary Care, University of Cambridge, UK

³Hull York Medical School, The University of Hull, Hull, UK

⁴Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford, UK

⁵Palliative and Supportive Services, Flinders University, Adelaide, Australia

⁶Division of Pulmonary, Critical Care, and Sleep Medicine, Beth Israel Deaconess Medical Centre, Boston, USA

⁷School of Nursing, Midwifery and Social Work, University of Manchester, Manchester, UK

⁸Centre for the Social History of Health and Healthcare, Glasgow Caledonian University, Glasgow, UK

⁹Centre for Medical Humanities, Durham University, Durham, UK

Title:

What's Trending in Breathlessness Research?

Proceedings from the 8th Annual Meeting of the Breathlessness Research Interest Group

7th November 2014

Institute of Public Health, University of Cambridge

Organised by the Cambridge Breathlessness Research Group, Drs Sara Booth & Morag Farquhar.

Authors: CA Chin¹, H Holt Butcher², A Spathis¹, R Ryan¹, M Johnson³, K Pattinson⁴, D Currow⁵, R Banzett⁶, J Yorke⁷, H Clayson⁸, J Macnaughton⁹, C Penfold², M Farquhar², S Booth¹

¹Department of Palliative Medicine, Addenbrooke's Hospital, Cambridge, UK

²Primary Care Unit, Department of Public Health & Primary Care, University of Cambridge, UK

³Hull York Medical School, The University of Hull, Hull, UK

⁴Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford, UK

⁵Palliative and Supportive Services, Flinders University, Adelaide, Australia

⁶Division of Pulmonary, Critical Care, and Sleep Medicine, Beth Israel Deaconess Medical Centre, Boston, USA

⁷School of Nursing, Midwifery and Social Work, University of Manchester, Manchester, UK

⁸Centre for the Social History of Health and Healthcare, Glasgow Caledonian University, Glasgow, UK

⁹Centre for Medical Humanities, Durham University, Durham, UK

Corresponding author: Dr Chloe Chin. chloe.chin@addenbrookes.nhs.uk

Palliative Medicine, Box 63, Elsworth House, Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Hills Road, Cambridge CB2 0QQ, UK.

Tel: 01223 274404

Co-authors:

Anna Spathis, Richella Ryan & Sara Booth at same address as corresponding author.

Hanne Holt Butcher, Clarissa Penfold & Morag Farquhar: Primary Care Unit, Department of Public Health & Primary Care, University of Cambridge, Institute of Public Health, Robinson Way, Cambridge CB2 0SR, UK

Miriam Johnson: Centre for Health & Population Sciences, Hull York Medical School, Heslington, York YO10 5DD, UK

Kyle Pattinson: Nuffield Department of Anaesthetics, Oxford University Hospital NHS Trust, John Radcliffe Hospital, Oxford OX3 9DU, UK

David Currow: Palliative and Supportive Services, Flinders University, GPO Box 2100, Adelaide 5001, South Australia

Bob Banzett: Division of Pulmonary and Critical Care KSB-26, Beth Israel Deaconess Medical Centre, 330 Brookline Avenue, Boston MA 02215-5491, USA

Janelle Yorke: School of Nursing, Midwifery and Social Work, University of Manchester, Room 5.320, Jean McFarlane University, University Place, Oxford Road, Manchester, M13 9PL, UK

Helen Clayson: Centre for the Social History of Health and Healthcare, Glasgow Caledonian University, Cowcaddens Road, Glasgow G4 0BA, Scotland

Jane Macnaughton: Centre for Medical Humanities, Durham University, Caedmon Building, Leazes Road, Durham DH1 1SZ, UK

Keywords: Breathlessness, Dyspnoea, Shortness of Breath, Neuroimaging, Non-pharmacological Intervention

Word count: 2241

Abstract/Summary

Breathlessness remains a challenging symptom, common to a multitude of malignant and non-malignant diseases, for which there are limited effective therapies once disease control is optimised. The American Thoracic Society (ATS) statement on dyspnoea reports that:

- i) Progress in dyspnoea management has not matched progress in elucidating underlying mechanisms;
- ii) There is a critical need for interdisciplinary translational research to connect dyspnoea mechanisms with treatments;
- iii) There is a need to validate dyspnoea measures as patient-reported outcomes for clinical trials.

Research into the many dimensions of breathlessness and its significance to patients and their carers has increased in recent years. This meeting is convened yearly to bring together researchers across various disciplines including respiratory medicine, anaesthetics, medical humanities, engineering and palliative care, to further understanding of the symptom, discuss new techniques and advances in research, and pave the way forward for future studies and interventions.

The presentations generated much vibrant discussion amongst the multidisciplinary attendees and highlighted areas where care for breathless patients could be improved. This is a positive time for breathlessness research, with several ATS research priorities being addressed and it is clear that further studies and ensuing interventions are on the horizon.

Breathlessness is a symptom common to a multitude of malignant and non-malignant diseases. Even once disease control is optimised, there are limited effective therapies for this challenging symptom. The American Thoracic Society (ATS) statement on dyspnoea reports that:

- i) Progress in dyspnoea management has not matched progress in elucidating underlying mechanisms;
- ii) There is a critical need for interdisciplinary translational research to connect dyspnoea mechanisms with treatments;
- iii) There is a need to validate dyspnoea measures for use as patient-reported outcomes in clinical trials.¹

Research into the many dimensions of breathlessness and its significance to patients and their carers has increased in recent years.² Although there are challenges to researching breathlessness, consensus does exist regarding a rational approach to designing adequately powered interventional studies, in order to allow future comparison between trials.³ This meeting is convened yearly to bring together researchers across various disciplines including respiratory medicine, anaesthetics, medical humanities, engineering and palliative care, to further understanding of the symptom, discuss new techniques and advances in research, and pave the way forward for future studies and interventions.

Presentation 1

Using MEG scanning to understand refractory breathlessness

Prof Miriam Johnson

Central (neural) mechanisms of breathlessness are yet to be fully understood. Although much has been elucidated with the advent of positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), most studies have been on healthy volunteers using models of induced acute breathlessness.⁴ Magnetoencephalography (MEG) scanning is a form of functional brain imaging which detects changes in magnetic fields generated by the electrical currents caused by neuronal activity. It therefore differs from fMRI where changes in brain activity are inferred from measured changes in blood flow due to altered metabolic activity. MEG has advantages in terms of better patient tolerability, such as the ability to sit upright in the machine, and it allows direct measurement of neuronal activity in response to the patient's circumstances for example, breathlessness induced by exercise which can be performed whilst seated in the scanner.

Professor Johnson's team are using MEG to study patients with chronic breathlessness and determine their neural responses to therapeutic interventions such as cool air across the face. They hope to develop methodology for future studies and confirm whether MEG imaging will be key to exploring the mechanisms by which patients perceive breathlessness.

Presentation 2

Neuroimaging of respiratory control in the human periaqueductal gray to understand brain mechanisms in breathlessness

Dr Kyle Pattinson

The brain is the final common pathway in various sensations such as pain, fear and breathlessness. Understanding the neural pathways involved will improve our understanding of breathlessness and therapies could potentially be targeted to these central mechanisms.⁴

The periaqueductal gray (PAG) is a small structure located superiorly in the brainstem and as it sits at a junction between the cortex and brainstem, is key in the emotional and mechanical control of breathing. We know from animal models that the PAG is involved in active and passive coping strategies and through connectivity to other parts of the brain, its activity can be up- or down-regulated in response to different situations such as pain or breath-holding.⁵ Until recently, there have been difficulties with poor resolution of functional imaging of the area to elucidate PAG activity. However, Dr Pattinson's group are investigating new imaging techniques including diffusion tractography (a form of MRI) to define PAG structure and activity and therefore provide greater understanding of the neurophysiology of breathlessness.⁶

Presentation 3

Pharmacological approaches to palliating breathlessness: what's new?

Prof David Currow

Professor Currow provided an update on the evidence basis for three interventions for breathlessness: oxygen therapy, opioids and benzodiazepines, and nebulised opioids, and challenged aspects of current clinical practice.

Most evidence suggests that oxygen does not have a role in the palliation of breathlessness.⁷ Professor Currow drew our attention to a Cochrane systematic review which favoured oxygen over air for the reduction of breathlessness in people with COPD who did not qualify for home oxygen.⁸ He also described a small study which showed that, although the majority of patients gained no additional symptomatic benefit from routine oxygen in the last hours or days of life, approximately 10% of patients used oxygen to relieve distress from dyspnoea, so there may be a role for oxygen in certain subgroups of patients.⁹

Opioids have a well-established role in the palliation of breathlessness, with most evidence supporting regular, low dose, sustained-release oral morphine. Professor Currow and colleagues have studied the effect of long-acting morphine on breathlessness and found benefit, in a phase 2 study up-titrating once daily sustained-release morphine, in approximately two-thirds of people.¹⁰ Until recently, there has been little evidence to support the safety of opioids in advanced respiratory disease. However, in a large cohort study of 2249 patients with very severe COPD, it was observed that opioids at lower dose (≤ 30 mg oral morphine per day) were not associated with increased mortality but higher doses were.¹¹ Benzodiazepines were associated with increased mortality with a dose response trend. Although this study could not ascribe causality, neither benzodiazepines nor opioids were associated with increased hospital admission rates, and whilst concurrent benzodiazepine with low dose opioid usage was not associated with increased mortality, higher doses were.¹¹

Finally Professor Currow briefly talked about nebulised morphine and its potential role as a treatment for breathlessness. Although current limited evidence does not support this treatment, a small study of patients with breathlessness secondary to mustard gas exposure found benefit from once daily nebulised morphine without significant adverse effects.¹²

Dyspnea: The First Vital Sign

Prof Bob Banzett

Professor Banzett proposed three “flavours” of dyspnoea which are described differently, manipulated independently and have different neural pathways.¹³ Dyspnoea is not a single sensation and can be thought of as comprising:

1. Air hunger,
2. Work/effort of breathing,
3. Chest tightness.

He affirmed the multidimensional nature of breathlessness with a sensory dimension and affective components. These include the distress caused by the unpleasantness of being breathless, and the emotional or evaluative responses that drive the accompanying feelings of fear and anxiety.¹⁴

He described experiments his team have undertaken which show that patients can reliably rate their breathing discomfort and that there is good day-to-day consistency. The American Thoracic Society emphasises that dyspnoea can only be perceived by the person experiencing it.¹ Interestingly, it has been shown that clinicians usually underestimate dyspnoea.¹⁵ Further experiments show that free breathing, even with increased inspired CO₂, is less uncomfortable than limited ventilation.¹⁶⁻¹⁸ Increasing a patient’s tidal volume relieves air hunger even when the ribcage and diaphragm are denervated due to cervical spine injuries.¹⁹ This supports the view that air hunger is a balance between respiratory drive and ventilation. Other experiments show that hypoxia must be profound to have significant effect on breathlessness.²⁰

Professor Banzett discussed the important evidence that dyspnoea is a better predictor of mortality and other adverse effects than FEV1 or other objective data.^{21,22} He described a pilot study in the USA involving nurses in a large teaching hospital in Boston recording dyspnoea in conjunction with the traditional vital signs. Efforts are being made to improve the methods used to measure dyspnoea and determine the ideal frequency of measurement.²³ Dyspnoea is becoming recognised as a ‘vital symptom’ that impacts on patient outcomes.

Presentation 4

A feasibility study to adapt and develop a breathlessness intervention service (BIS) for people suffering from asbestosis in India: The SHWASS project

Dr Helen Clayson

Dr Clayson described a community-based volunteer-led educational programme using evidence-based, low-cost, low-technology, non-pharmacological interventions to try to improve breathlessness in former asbestos industry workers with asbestosis in Mumbai. The interventions trialled include exercise, fans, breathing control, positioning techniques, social support. They were evaluated with objective measures such as the 6-minute walk test and pulmonary function tests, as well as qualitative methods such as questionnaires and interviews. The project is still in progress and full evaluation has yet to be completed. However, there have been many learning points already including the importance of understanding cultural differences and how these affect research.

Presentation 5

Developing a complex non-pharmacological intervention for the respiratory symptom cluster of breathlessness, cough and fatigue in lung cancer

Dr Janelle Yorke

In lung cancer, the respiratory distress symptom cluster of breathlessness, cough and fatigue has been described by Molassiotis et al with breathlessness usually being the driving symptom of the cluster.²⁴ An evidence base is developing for non-pharmacological management of single symptoms, but few have been developed and evaluated for symptom clusters. Given that the symptoms are usually present together, there is an argument that interventions should be targeted towards managing them concurrently in order to improve patients' quality of life. Ellis et al have interviewed patients and results revealed that they would want flexible, practical interventions that would provide strategies to cope with different symptoms and specific problems, and that caregivers could be taught to carry out.²⁵ This information aided development of a complex intervention for which Dr Yorke's group have recently completed a study evaluating its feasibility and acceptability in management of the respiratory distress symptom cluster. Results are encouraging and warrant further investigation in a fully powered randomised controlled trial.

Presentation 6

The Life of Breath: A Medical Humanities approach to breathlessness.

Prof Jane Macnaughton

A medical humanities approach takes the view that biomedicine is unable to encompass and describe all aspects of breathlessness as there are significant emotional and existential components to the experience of this symptom. These components may, for example, be reflected in the metaphors exist surrounding breath, such as the first and last breath representing birth and death. The Wellcome Trust-funded Life of Breath project, which is a collaboration between Professor Macnaughton and Professor Havi Carel in Bristol, aims to provide an interdisciplinary understanding of the experience of breathing and breathlessness by bringing together historical, philosophical, anthropological and clinical research. It will investigate the cultural significances and historical origins of attitudes towards breathing, public health relationships, explore the phenomenology of breathing and breathlessness, and non-pathological versus pathological breathlessness. The aim is to impact upon the ways in which research on this symptom is carried out, and ultimately upon care and treatment.

Presentation 7

Data from the Living with Breathlessness study in COPD

Dr Morag Farquhar

The trajectory of COPD is that of a slow decline punctuated by acute exacerbations and contrasts significantly with that of lung cancer. There is a lack of research into the non-malignant disease trajectory. Dr Farquhar outlined the methods and components of the Living with Breathlessness study programme which seeks to address this knowledge gap, and presented baseline results from one component: the Longitudinal Interview Study. This is a mixed methods longitudinal study of a population-based cohort of 235 patients and 117 informal carers. The

patients had moderate to severe breathlessness as characterised by mean MMRC dyspnoea scale and COPD Assessment Test (CAT). Patients experienced multiple symptoms including fatigue, cough, pain, anxiety, and depression. A notable proportion of these symptoms were not reported to a healthcare professional: anxiety and depression in particular. The needs of informal carers are also being investigated using the Carer Support Needs Assessment Tool (CSNAT) alongside other carer variables such as their preparedness for caregiving. Dr Farquhar presented findings on patients' service access and views of care. The research aims to identify drivers for service delivery as well as met and unmet needs amongst patients and carers.

Presentation 8

Learning about breathlessness study

Dr Clarissa Penfold

Breathlessness is a distressing, disabling symptom of advanced disease with considerable impact on informal carers. Carers experience anxiety, isolation, restriction of activity, lack of support and powerlessness. The Learning about Breathlessness study, led by Dr Morag Farquhar, seeks to understand educational needs of carers. In particular, the study is exploring carer preferences for learning content and delivery modes for an educational intervention to support informal carers and enhance their caregiving capacity. Qualitative in-depth interviews were conducted with a purposive sample of 24 patient-carer dyads. Despite different disease trajectories (cancer and COPD), preliminary results suggest that there are similarities in carer preferences for content and delivery mode. Workshops with clinical-practitioner experts and informal carers will draw on these interview findings to co-develop an educational intervention. Finally, an online survey of clinicians will identify clinician-relevant outcomes for a future RCT of the co-developed intervention.

Presentation 9

Brief update on breathlessness and its relationship with the HPA axis

Dr Richella Ryan

Breathlessness tends to be experienced as a threat to survival, suggesting involvement of the stress system. Dr Ryan and her colleagues are exploring the role of the hypothalamic-pituitary-adrenal (HPA) axis in breathlessness, hypothesising that chronic breathlessness causes over-activation of the HPA axis, with resultant dysregulation of diurnal cortisol secretion. They are currently conducting a feasibility study in which salivary diurnal cortisol levels are measured in patients with chronic breathlessness, both before and after an intervention (ISRCTN70836126). Though this is early work, it is exciting to consider the potential of this system as a biomarker for the evaluation of breathlessness therapies within clinical trials.

Conclusion

This meeting demonstrates the wide variety of research being carried out in the field of breathlessness addressing a spectrum of issues from understanding biological mechanisms to patient and carer experiences, and attempting to disseminate the knowledge to communities with fewer resources. Each year more areas of research are introduced and progress in managing the symptom is evident. However, breathlessness management and research still lags behind that for other symptoms such as pain, and larger studies in different subgroups of patients are needed. The

presentations generated vibrant discussion amongst the multidisciplinary attendees and highlighted areas where care for breathless patients could be improved. This is a positive time for breathlessness research, with several of the ATS research priorities being addressed and it is clear that further important studies and innovative interventions are on the horizon.

Acknowledgments:

The meeting was organised by Drs Sara Booth and Morag Farquhar with many thanks to the co-authors for their interesting presentations and input regarding this article.

Competing interests:

There are no competing interests of note.

Funding:

No funding required.

References:

1. Parshall MB, Schwartzstein RM, Adams L et al. American Thoracic Society Committee on Dyspnea. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med* 2012; 185:435-52
2. Gray JE, Booth S, Brage S et al. Meeting report of Breathlessness Research Interest Group. *Prog Palliat Care* 2010; 18: 95-98
3. Dorman S, Jolley C, Abernethy A et al. Researching breathlessness in palliative care: consensus statement of the National Cancer Research Institute Palliative Care Breathlessness Subgroup. *Palliat Med* 2009; 23:213-227
4. Pattinson KT, Johnson MJ. Neuroimaging of central breathlessness mechanisms. *Curr Opin Support Palliat Care* 2014; 8:225-33
5. Pattinson KT, Governo RJ, MacIntosh BJ et al. Opioids depress cortical centres responsible for the volitional control of respiration. *J Neurosci* 2009; 29:8177- 8186
6. Faull OK, Jenkinson M, Clare S, Pattinson KT. Functional subdivision of the human periaqueductal grey in respiratory control using 7 tesla MRI. *Neuroimage* 2015. S1053-8119(15)00127-5. doi: 10.1016/j.neuroimage.2015.02.026 Epub ahead of print.
7. Abernethy AP, McDonald CF, Frith PA et al. Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnoea: a double-blind, randomised controlled trial. *Lancet* 2010; 376:784-93
8. Uronis H, McCrory DC, Samsa G et al. Symptomatic oxygen for non-hypoxaemic COPD. *Cochrane Database Syst Rev* 2011; 15:CD006429
9. Campbell ML, Yarandi H, Dove-Meadows E. Oxygen in nonbeneficial for most patients who are near death. *J Pain Symp Manage* 2013; 45:517-23
10. Currow DC, McDonald C, Oaten S et al. Once-daily opioids for chronic dyspnoea: a dose increment and pharmacovigilance study. *J Pain Symp Manage* 2011; 42:388-99
11. Ekstrom MP, Bornefalk-Hermansson A, Abernethy AP et al. Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. *BMJ* 2014; 30:348:g445
12. Shohrati M, Ghanei M, Harandi AA et al. Effect of nebulized morphine on dyspnea of mustard gas-exposed patients: a double-blind randomised controlled clinical trial study. *Pulm Med* 2012; 2012:610921
13. Gilman SA, Banzett RB. Physiologic changes and clinical correlates of advanced dyspnea. *Curr Opin Support Palliat Care* 2009; 3:93-7
14. Lansing, RW, Gracely RH, Banzett RB. The multiple dimensions of dyspnea: review and hypotheses. *Respir Physiol Neurobiol* 2009; 167:53-60
15. Hayes AW, Philip K, Spruyt OW. Patient reporting and doctor recognition of dyspnoea in a comprehensive cancer centre. *Intern Med J* 2006; 36: 381-4
16. Harty HR, Mummery CJ, Adams L et al. Ventilatory relief of the sensation of the urge to breathe in humans: are pulmonary receptors important? *J Physiol* 1996; 490: 805-15
17. Bloch-Salisbury E, Spengler CM, Brown R et al. Self-control and external control of mechanical ventilation give equal air hunger relief. *Am J Respir Crit Care Med* 1998; 157:415-20
18. Banzett RB, Lansing RW, Evans KC et al. Stimulus-response characteristics of CO₂-induced air hunger in normal subjects. *Respir Physiol* 1996; 103:19-31
19. Manning HL, Shea SA, Schwartzstein RM et al. Reduced tidal volume increase 'air hunger' at fixed PCO₂ in ventilated quadriplegics. *Respir Physiol* 1992; 90:19-30

20. Moosavi SH, Golestanian E, Binks AP et al. Hypoxic and hypercapnic drives to breathe generate equivalent levels of air hunger in humans. *J Appl Physiol* 2003; 94:141-54
21. Nishimura K, Izumi T, Tsukino M et al. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. *Chest* 2002; 121:1434-40
22. Banzett RB, O'Donnell CR. Should we measure dyspnoea in everyone? *Eur Respir J* 2014; 43:1547-50
23. Baker K, Barsamian J, Leone D et al. Routine dyspnea assessment on unit admission. *Am J Nurs* 2013; 113:42-9
24. Molassiotis A, Lowe M, Blackhall F et al. A qualitative exploration of a respiratory distress symptom cluster in lung cancer: cough, breathlessness and fatigue. *Lung cancer* 2011; 71:94-102
25. Ellis J, Wagland R, Tishelman C et al. Considerations in developing and delivering a nonpharmacological intervention for symptom management in lung cancer: the views of patients and informal caregivers. *J Pain Symptom Manage* 2012; 44: 831-42

Response to reviewers:

Reviewer #1: very interesting summary of innovative research in breathlessness.

My only concern is a sentence in the summary of presentation 3 which I consider potentially misleading. ".....neither benzodiazepines nor opioids were associated with increased hospital admission rates, and concurrent benzodiazepine with low dose opioid usage was not associated with increased mortality"

A more balanced summary should mention the significantly increased all-cause mortality risk with 'higher' benzodiazepine and opioid doses. Also that these "higher" doses were fairly modest (>3 mg of oral diazepam equivalents per day and >30 mg oral morphine equivalents per day).

We acknowledge Reviewer #1's comments and have revised the paragraph in question:

Opioids have a well-established role in the palliation of breathlessness, with most evidence supporting regular, low dose, sustained-release oral morphine. Professor Currow and colleagues have studied the effect of long-acting morphine on breathlessness and found benefit, in a phase 2 study up-titrating once daily sustained-release morphine, in approximately two-thirds of people.¹⁰ Until recently, there has been little evidence to support the safety of opioids in advanced respiratory disease. However, in a large cohort study of 2249 patients with very severe COPD, it was observed that opioids at lower dose (≤ 30 mg oral morphine per day) were not associated with increased mortality but higher doses were.¹¹ Benzodiazepines were associated with increased mortality with a dose response trend. Although this study could not ascribe causality, neither benzodiazepines nor opioids were associated with increased hospital admission rates, and whilst concurrent benzodiazepine with low dose opioid usage was not associated with increased mortality, higher doses were.¹¹

Reviewer #2: This paper is a description of several conferences from a meeting about dyspnoea. Thus, the paper describes the speakers' opinion and it shows a group of expert review but they are not a systematic review of diagnoses and treatment approaches. Therefore, it is difficult to appreciate the manuscript like a research paper.

This paper is not a review paper of diagnoses and treatment approaches to breathlessness, and is a report of a meeting describing various aspects of research in breathlessness.

Progress in Palliative Care ("the Journal")

ASSIGNMENT OF COPYRIGHT

In order for W S Maney & Son Ltd, trading as Maney Publishing ("the Publisher"), to ensure the widest possible dissemination and protection of articles published in the Journal, we request authors to assign worldwide copyright in print, digital and other media in their article, including abstracts, to W. S. Maney & Son Ltd. This enables the Publisher to ensure maximum international copyright protection against infringement, and to disseminate your article, and the Journal, to the widest possible worldwide readership. Should the article be rejected from the Journal for any reason, all rights assigned within this document revert back to the author(s) of the article

Please read the explanatory notes of this agreement on the following page.

1. In consideration of the undertaking set out in paragraph 2, the author(s) as beneficial owner(s) hereby assign(s) to W. S. Maney & Son Ltd all rights, title and interest in the copyright throughout the world in the article named below (which shall be taken to include any or all supplementary material associated with the article*) for the full legal term of copyright.

CA Chin, H Holt-Burton, A Spottis, R Ryan, M Johnson, K Parthasarathy, D Curran, R Barzlett, J Yakes, H Clayton, J Macdonald, C Perfol, M Fargnoli, S Booth

← Name(s) of Author(s)

Manuscript no./ref. (if known) PPC 252

If this paper is sponsored for Open Access by your grant funders, please follow the MORE OpenChoice route by signing and returning this copyright assignment to the address below, and find details of the policy and how to make payment at www.maneyonline.com/openaccess.

So that there should be no doubt, it is understood and agreed that this assignment includes the right to publish or adapt (subject to paragraphs 3 and 4) the material in the article for use in conjunction with computer systems, including networks. The article may be published in printed, CD-ROM, microfiche, on-line, or other machine-readable form, or in any other format or medium (electronic or otherwise) approved by W. S. Maney & Son Ltd, and subject to data mining.

Maney Publishing, as the Journal's publisher, hereby undertakes to prepare for publication and publish in the Journal, the Article named in paragraph 1.

The editor of the Journal, and the Publisher, are empowered to make such editorial changes as may be necessary to make the Article suitable for publication. Every effort will be made to consult the Author(s) if substantive changes are required.

The author(s) hereby assert(s) their moral rights under the terms of the Copyright Designs and Patents Act 1988 to be identified as the Author(s) of the Article.

The author(s) warrant(s) that the article is the author(s)' original work, has not been published before, either in part or whole, and is not currently under consideration for publication elsewhere. The author(s) also warrant(s) that (a) the article contains no libellous or unlawful statements, (b) it in no way infringes the rights of others (including the holders of copyright in material used within the article), (c) that permission has been obtained to reproduce any material or illustrations for which they do not hold copyright, and that (d) the author(s), as the owners of the copyright, is (are) entitled to make the assignment set out in this agreement. The author(s) hereby indemnifies/indemnify the Publisher against any claims for breach of the warranties given above.



Maney Publishing

Research • Knowledge • Innovation

www.maneypublishing.com

6. In cases where the article is a translation of a previously published article, the author(s) warrant(s) that full permission has been obtained to carry out and publish the translation of the article from its original language, and that it in no way infringes the rights of others (including the holders of copyright in material used within the original Article).
7. The author(s) warrant(s) that the article contains no plagiarised material and agree(s) that the article may be checked for plagiarism and other ethical questions (including checks using automated software packages). The Publisher reserves the right to withdraw or retract any article for which, in its reasonable opinion, valid concerns exist over the originality of the article, or its compliance with the Journal's ethical policy. Maney's plagiarism and ethical policy may be read in full at www.maneyonline.com/page/authors/publishingethics-general.

*If the author(s) cannot assign copyright for any or all the supplementary material, the clause in parentheses should be struck out and a licence to publish provided for this material. If copyright is held by a third party, permission to reproduce this material must be obtained from the copyright holder as laid out in paragraph 5 of this form and submitted to the publisher.

Copyright Assignment

I confirm that all the co-authors, named above in 1, know that the article has been submitted to the Journal.

I hereby sign this Assignment of Copyright with the full knowledge and agreement of all authors.

Signed:

OR CHWEE A CHIN

Date:

13/4/15

Printed name: *OR CHWEE A CHIN*

Please note: it is essential for publication that Maney Publishing receive this signed Assignment of Copyright form. Without it, we will be unable to proceed to publication.

Please complete all specified fields and return this signed form to the Production Editor of the Journal.

Production Editor, PPC, for Maney Publishing
ppc@maneypublishing.com; fax: +44 (0) 20 7451 7307
1 Carlton House Terrace, London SW1Y 5AF, UK