
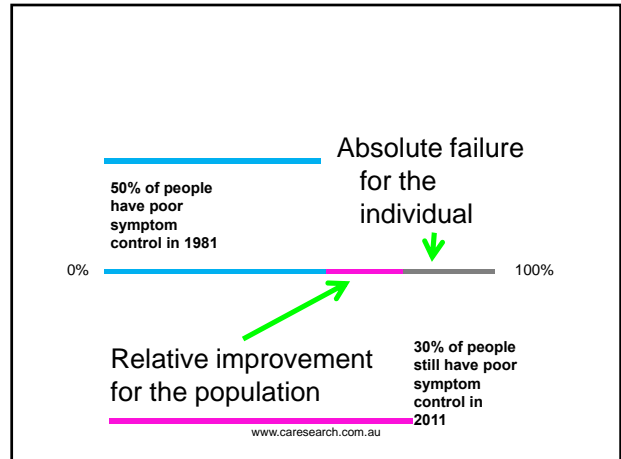



Professor David C Currow

**Discipline, Palliative and Supportive Services,
Flinders University.
Adelaide
Australia**

**'It's funny, but you never think much about breathing.
Until it's all you ever think about.'**

'Breath'
Tim Winton, Penguin 2008



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Magnitude of problem – whole of population

(Population estimates that do not rely only on health service attendance)

Modified Medical Research Council Scale

- 1% of the population had chronic disabling dyspnoea (mMRC ≥ 3).
- 0.3% of people were housebound by breathlessness

Currow et al. J Pain Symptom Manage, 2009; Hammond E. Am J Publ Health 1964



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Magnitude of problem – whole of population

Multifactor analysis delineating demographic associations with significant breathlessness (MRC ≥ 2)

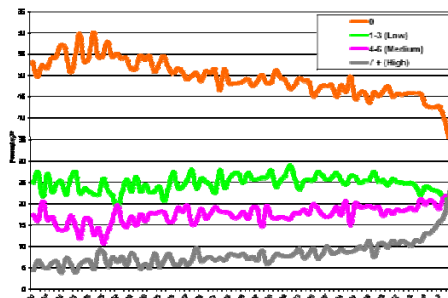
Female	OR 1.8	p<0.001
Low income	OR 2.0	p=0.007
Work related injury	OR 3.5	p<0.001

Currow et al. J Pain Symptom Manage 2009

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116,982 data points in 5,862 people

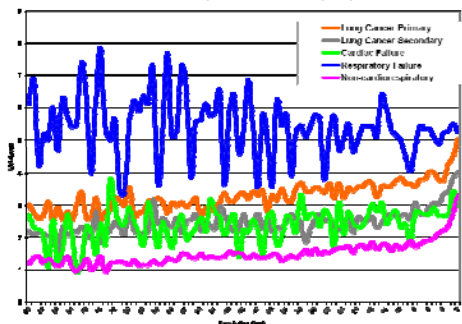


Currow et al JPSM. 2010;39(4):680-690

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116,982 data points in 5,862 people



Currow et al JPSM. 2010;39(4):680-690

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Prevalence of pathology

100 consecutive patients with cancer

- Median VAS dyspnoea **53mm**
- Spirometry abnormal **93%**
 - 5% obstructive; 41% restrictive; 47% mixed
- Mean max. inspiratory pressure **16cm H₂O**
 - >80 – no significant weakness
 - <50 – impaired ability to generate cough to clear secretions
- No chest x-ray abnormality **35%**
- Recent ischaemia, infarct or AF **29%**

Dudgeon D, Lertzman M. Dyspnea in the advanced cancer patient. J Pain Symptom Manage 1998;16(4):212-219.



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Prevalence of potentially contributing / reversible causes


100 consecutive patients with cancer

- Median of 5 likely contributing causes


- Potentially correctable causes

hypoxaemia	40%
anaemia	20%
bronchospasm	52%


Dudgeon D, Lertzman M. Dyspnea in the advanced cancer patient. J Pain Symptom Manage 1998;16(4):212-219.



1. What were we saying a decade ago?
2. What level I and II evidence has emerged in the last decade?
3. What correlative science have we seen?
4. What is the research agenda moving forward?



1. What were we saying a decade ago?



What were we saying a decade ago?

- Oxygen therapy in 'hypoxemic and nonhypoxemic patients'
- Transfusion therapy 'controversial'
- Oral, parenteral opioids but not nebulized
- Benzodiazepines ineffective in 4/5 trials
- Focus on breathlessness as a symptom rather than a function simply of gas exchange
- Use allied health interventions

Ripamonti C. Support Care Cancer. 1999;7(4):233-243.



2. What level I and II evidence has emerged in the last decade?



Opioid therapy – meta-analysis

- Jennings et al *Thorax* 2002
- Cochrane meta-analysis of double-blind randomized placebo-controlled trials of opioids in refractory dyspnoea of 9 studies with 116 participants

- P - Dyspnoea due to any cause
- I - Parenteral / oral opioids
- C - Placebo
- O - Dyspnoea intensity

Results - Dyspnoea intensity reduced by 8mm on 0-100mm scale with a mean starting point of 50mm (16% improvement)
Magnitude of benefit maintained for people with COPD



Opioid therapy

- Abernethy et al *Br Med J* 2003

- P - 48 opioid naïve patients with dyspnoea due to any cause*
- I - Morning sustained release morphine 20mg / 24 hours
- C - Placebo
- O - Dyspnoea intensity at day 4

Double-blind randomised cross-over
Results - Dyspnoea intensity reduced by 7 – 10 mm on 0-100mm scale with a mean starting point of 47mm (15 - 22% improvement)

*88% had COPD as their primary cause of breathlessness



Dyspnoea - Opioid therapy

Open label cohort study - Phase II / IV
31 participant/years of data from 85 participants
For initial response (Phase II):-

- Number needed to treat – 1.6 (2.1 at 3/12)
- Of responders, 92% responded at 20mg / 24 hours or less.
- Number needed to harm – 4.5

No evidence of tachyphylaxis (mean 132 days follow up)
No respiratory-related hospitalisations

Currow DC et al. Once-daily opioids for chronic dyspnoea: a dose increment and pharmacovigilance study. J Pain Symptom Manage [Epub ahead of print 2011 March 30].



- Khan et al. BMC Pulm Med 2004

- D - Single blind assessment of sham versus effective administration of nebulised saline at 10 minutes
- P - 40 patients FEV₁ 30%, in hospital with acute exacerbation
- I - Nebulised saline
- C - Ineffectively nebulised saline
- O - Intensity of breathlessness on a Likert scale

No significant difference in FEV₁ (can therefore be used as a control arm in bronchodilator studies)

4% vs 23% improvement in breathlessness (p=0.0001) (cannot be used as a placebo arm in studies of nebulised medications)
5% vs 65% improvement in mucous expectoration (p<0.0001)

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Non-pharmacological / non-oxygen interventions 2532 participants in 47 studies:

walking aids (7); music (6); chest wall vibration (5);
acupuncture / acupressure (5); relaxation (4);
neuro-electrical muscle stimulation (3); fan (2);
counselling (6); breathing training (3); counselling
and support (2); case management (2);
psychotherapy (2).

Bausewein et al Cochrane Collaboration, 2008

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Non-pharmacological / non-oxygen interventions

2532 participants in 47 studies:

Strong evidence of benefit:

- chest wall vibration (5);
- neuro-electrical muscle stimulation (3).

Moderate strength of evidence:

- walking aids (7); - breathing training (3).

Bausewein et al Cochrane Collaboration, 2008

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- Uronis et al *Cochrane database of systematic reviews* 2011
Mean study quality score 2.9

D - Cochrane review of symptomatic benefit of oxygen in people with COPD of 18 studies and 321 participants

P - People with COPD (mean FEV₁ 0.9l) who do NOT qualify for domiciliary O₂


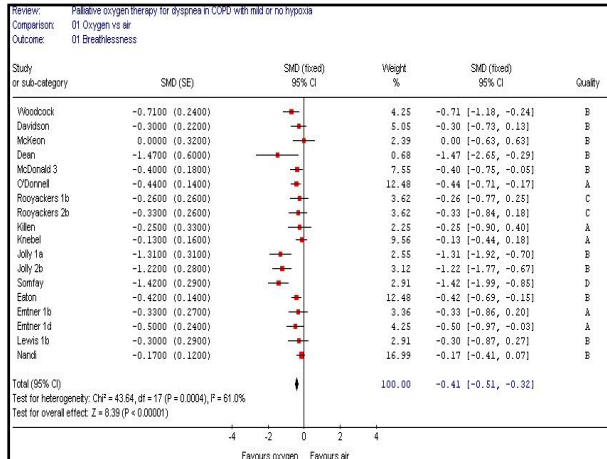
I - Oxygen therapy (short burst and long term)

C - Medical air

O - Breathlessness (visual analogue, numerical rating or Borg)

Results. Reduced standardised mean difference of breathlessness -0.41 (95% CI -0.52 to -0.33). All studies reduced breathlessness

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- Uronis et al Br J Cancer 2008
Mean study quality score 2.1

D - Cochrane review of symptomatic benefit of oxygen in people with cancer who do not qualify for domiciliary oxygen

P - People with cancer who do NOT qualify for domiciliary O₂ (Mean pulse oximetry 93%)


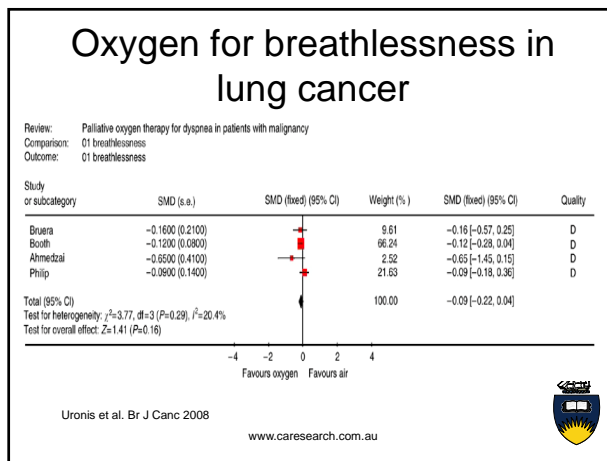
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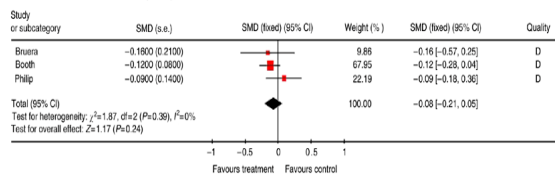
Results. Reduced standardised mean difference of breathlessness (SMD 0.08, 95% CI -0.22 to 0.05; p=0.24).

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Oxygen for breathlessness in lung cancer

Review: Palliative oxygen therapy for dyspnea in patients with malignancy
 Comparison: O1 breathlessness
 Outcome: O2 breathlessness no imputed quantities



Uronis et al. Br J Canc 2008

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Abernethy et al. Lancet 2010

- P - People with refractory dyspnoea who do not qualify for oxygen
- I - Oxygen (2l/min for >15 hours per day for one week)
- C - Medical air
- O - average breathlessness on numerical rating scale over the last 3 days of the intervention arm

Results oxygen was not superior to air, although both were superior to baseline. Oxygen of more benefit in the morning (dose /response relationship?); highest levels of baseline breathlessness

Responders (blinded) more likely to want to continue therapy (51% vs 39%; $p=0.08$)

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3. What correlative science have we seen?



Dyspnoea Opioid therapy

- Mahler et al *Eur Resp J* 2009

- P - 17 people with moderate to severe COPD
- I - Naloxone 10mg i.v. before constant intense work rate on treadmill for a minimum of 10 minutes
- C - Normal saline
- O - Oxygen use / breathlessness regression curve; breathlessness scores

Double blind randomised crossover

Results – significantly increased breathlessness / oxygen consumption regression curve in naloxone group; significantly less breathlessness in saline group



...the sensation

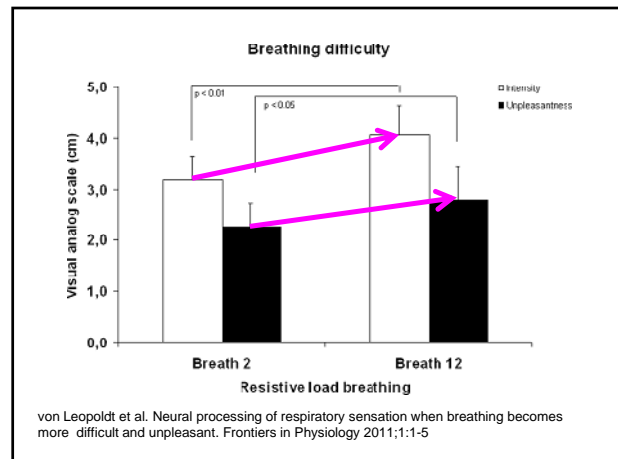
Intensity of breathlessness is probably what we ask patients

But there is good evidence that the *intensity* may be less important than *how unpleasant the sensation is*

Intensity and *unpleasantness* may potentially even respond differently to symptom control interventions.

Lansing et al, Resp Physiol Neurobiol 2009, von Leopoldt et al. Chest 2005, Williams Chest 2010

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4. What is the research agenda moving forward?



What is the research agenda moving forward?

1. Effectiveness data to match efficacy data
2. Need to explain variations in response to symptomatic therapies across the population to target treatments more effectively
3. More collaboration with our laboratory colleagues
4. More systematic evaluation of the net benefit of allied health input to the management of dyspnoea
5. A good phase III study on the role of benzodiazepines and other candidate therapies for which there are good pilot data
6. Evidence into practice for a generation of clinicians for whom breathlessness is still simply a clinical sign



**What were we saying a decade ago?
What has changed?**

For patients?

In the evidence base?

