

# Managing breathlessness

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breathlessness

**‘It’s funny, but you never think much  
about breathing..**

**‘Breath’**

**Tim Winton, Penguin 2008**



breathlessness

**‘It’s funny, but you never think much  
about breathing...  
until it’s all you ever think about.’**

**‘Breath’**

**Tim Winton, Penguin 2008**



# Improving breathlessness

- 1. The symptom burden of breathlessness and its measurement**
- 2. Management of breathlessness**
  - 1. Consensus statements**
  - 2. Non-pharmacological interventions**
  - 3. Opioids**
  - 4. Oxygen**



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# Deconstructing breathlessness ...the *sensation*

- **‘Neuroventilatory dissociation’**
- **‘Efferent / reafferent dissociation’**
- **‘Mismatch theory’**
  
- **Afferent stimuli (mechanical, chemical) generate an efferent response that does not sufficiently reduce the afferent stimuli**

O'Donnell et al. Am Rev Resp Dis 1993



# breathlessness

**Magnitude of problem – whole of population**

## **Community breathlessness**

	<b>Women</b>	<b>Men</b>
<b>Never</b>	<b>74.8%</b>	<b>84.2%</b>
<b>Incident</b>	<b>13.6%</b>	<b>7.7%</b>
<b>Remission</b>	<b>4.7%</b>	<b>3.8%</b>
<b><i>Persistent</i></b>	<b><i>6.9%</i></b>	<b><i>4.3%</i></b>



# breathlessness

## **Magnitude of problem – whole of population**

**n = 8,396**

### **Modified Medical Research Council (mMRC) Scale**

**- 8.9% overall at  $\geq 2$**

**- 1% of the population had chronic disabling breathlessness (mMRC  $\geq 3$ ).**

**- 0.3% of people were housebound by breathlessness (mMRC = 4)**





# breathlessness

## Magnitude of problem – whole of population

### Multifactor analysis

Demographic associations with significant breathlessness (mMRC  $\geq 2$ )

<b>Female</b>	<b>OR 1.8</b>	<b>p&lt;0.001</b>
<b>Low income</b>	<b>OR 2.0</b>	<b>p=0.007</b>
<b>Work related injury</b>	<b>OR 3.5</b>	<b>p&lt;0.001</b>



# breathlessness

## **Magnitude of problem – whole of population**

**Health Omnibus; n=4432**

**To what do people attribute their  
breathlessness?**

**If breathless (mMRC  $\geq 1$ ), then 65% of people  
attributed their breathlessness to lung  
disease**

**If attributed to lung disease, it was likely that  
breathlessness had been with them for  
significantly longer –**

**13.8 yrs vs 5.7 yrs;  $p < 0.001$**



# breathlessness

**Magnitude of problem – whole of population**

**E. Cuyler Hammond**

**#3 on the list of factors associated with increased mortality (by Oct 1, 1962)**

**Mortality ratio (O/E)**

**Loss of weight 2.24**

**Loss of appetite 2.14**

***Shortness of breath 2.08***



# breathlessness

## Breathlessness as a predictor of death

n = 754 >70, mobile, living at home

589 participants died between October 1998 and June 2013,  
41 had withdrawn from the study, leaving 548 (93%) with  
data on breathlessness.

Monthly phone interviews

Participants were asked if they had stayed in bed at least half  
a day or cut down on their usual activities due to an illness,  
injury, or other problem in the preceding month.

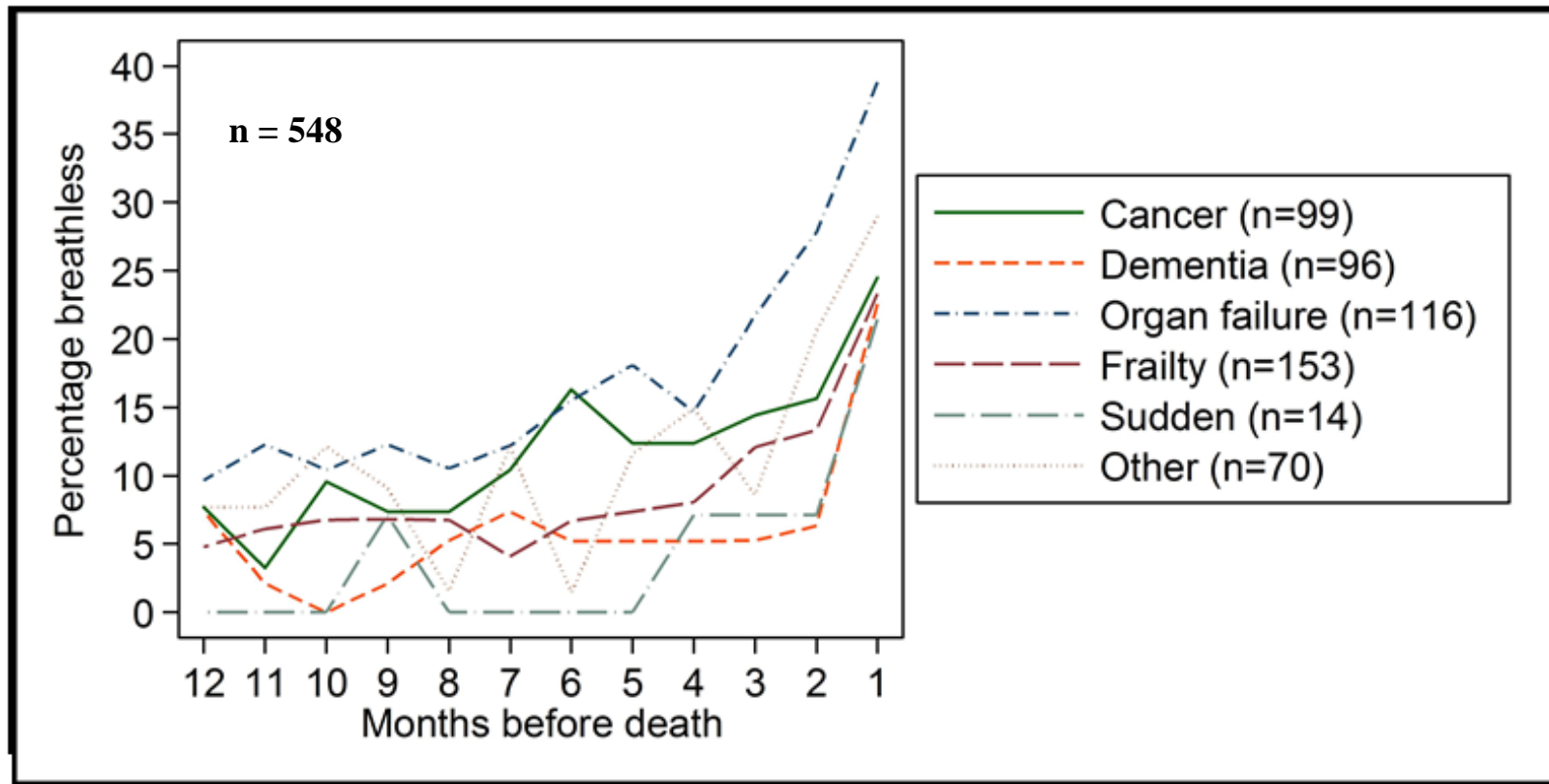
Those who said 'yes' to either question were asked whether  
they had experienced "difficulty breathing or shortness of  
breath since we last talked" *and* whether or not that problem  
caused restricted activity.



# breathlessness

## Breathlessness as a predictor of death

The percentage of participants reporting restricting breathlessness at each month during the last year of life by condition leading to death



# Patient reporting versus doctor recognition of breathlessness in a cancer centre



Hayes A W et al. *Int Med J* 2006

D – cross-sectional prevalence survey of any breathlessness in the preceding 24 hours for inpatients at a cancer hospital. Simultaneous perceptions of junior medical staff providing direct care

P – 100 patients (of 115 who were in hospital: 15 had language or cognitive barriers)

## **Patient self-report:**

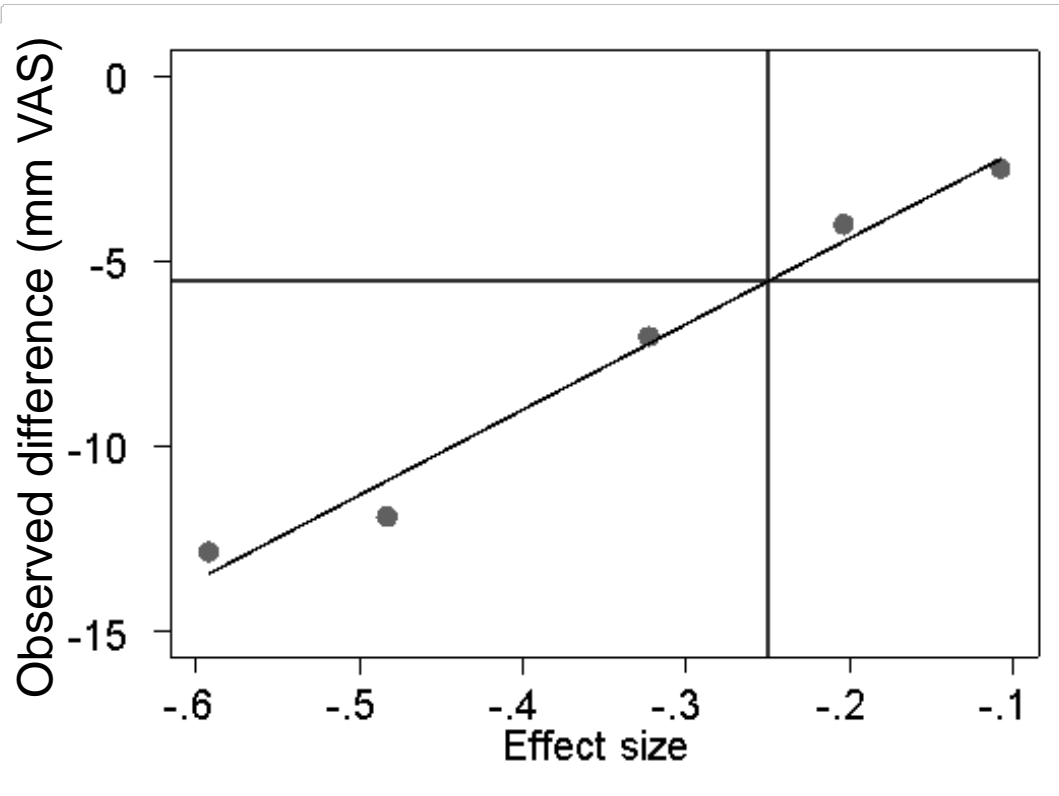
- Prevalence 33% with potentially reversible causes in 15.
- 24/33 (73%) identified breathlessness *intensity* as ‘moderate’ or ‘severe’
- 18/33 (55%) identified breathlessness *distress* as ‘moderate’ or ‘severe’

## **Junior medical officer report:**

- Unrecognised by junior medical staff in 9 patients (p=0.021)
- breathlessness *intensity* rated as ‘moderate’ or ‘severe’ in only 12 cases
- breathlessness *distress* rated as ‘moderate’ or ‘severe’ in only 10 cases

## Minimum clinically important difference in chronic breathlessness

Regression line of effect size (change in VAS score divided by standard deviation of baseline scores) and patient rated change in breathlessness score (VAS)



**Effect size for VAS change:**

**Small (0.25): -5.5mm**

**Medium (0.5): -11.3mm**

**Large (0.8): -18.2mm**

**Patient-anchored data  
-8.9mm**

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# breathlessness

## **New guidelines for the symptomatic treatment of breathlessness in advanced lung or heart disease – American College of Chest Physicians**

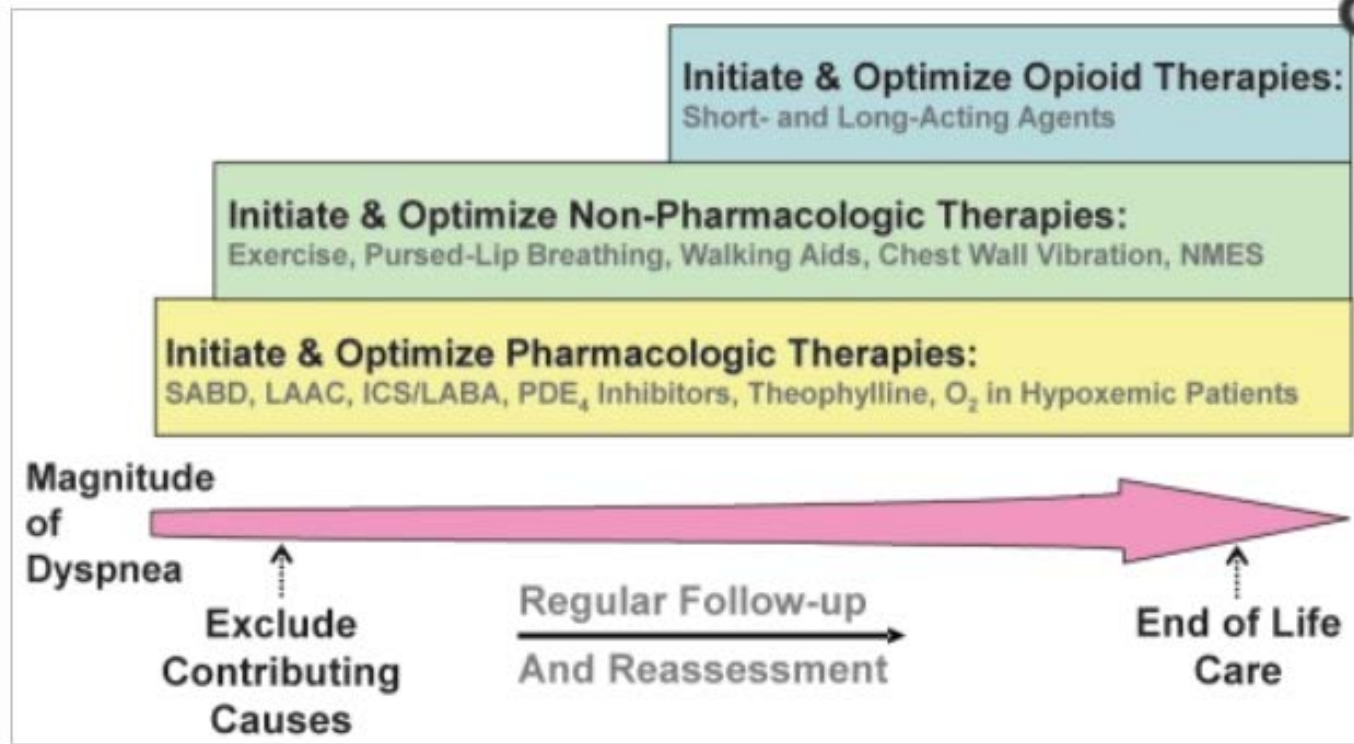
- ‘...dyspnea that persists at rest or with minimal activity and is distressful despite optimal therapy of advanced lung or heart disease...’
- ‘...health-care professionals are ethically obligated to treat dyspnea...’
- ‘...opioids should be dosed and titrated for relief of dyspnea in the individual patient...’



# breathlessness

## New guidelines for managing breathlessness in COPD – Canadian Thoracic Society clinical practice guideline

‘... The evidence supports the benefits of oral opioids...’



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# Non-pharmacological 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).**



# Non-pharmacological 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).



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**‘Of all the remedies it has  
pleased almighty God to give  
man to relieve his suffering,  
none is so universal and so  
efficacious as opium’**



***Thomas Sydenham 1624-1689***

***‘the English Hippocrates’***



# breathlessness

## Opioid therapy

- Mahler et al *Eur Resp J* 2009

- D - Double blind, randomised crossover
- 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

Results – In the naloxone arm, significantly increased:

- breathlessness / oxygen consumption regression curve
- peak breathlessness; and
- mean breathlessness throughout exercise





# Opioid therapy in COPD

Ekström et al. *Ann Am Thoracic Soc* 2015

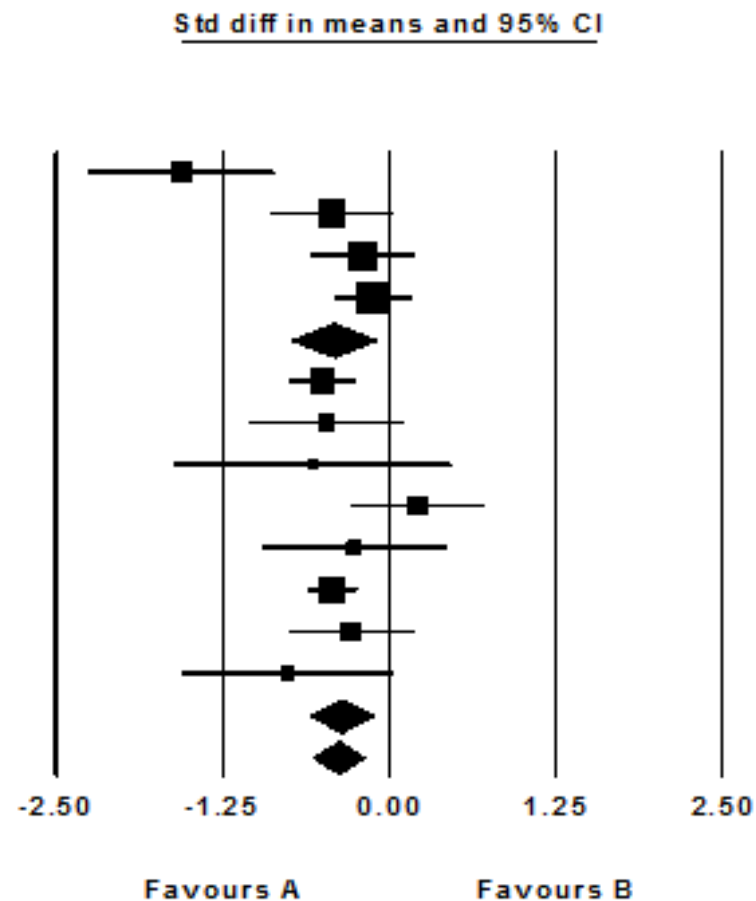
- Review of double-blind randomised trials of opioids in refractory breathlessness in people with COPD.
- 16 studies (15 cross over, one parallel arm) with 271 participants
- D - Meta-analysis
- P - breathlessness due to COPD
- I - Opioids
- C - Placebo
- O - Breathlessness, exercise capacity, quality of life





# Opioid therapy in COPD - breathlessness

Group by Comparison	Study name	Comparison	Std diff in means	Lower limit	Upper limit
Nebulized	Shorati, 2012	Nebulized	-1.56	-2.27	-0.85
Nebulized	Jensen, 2012	Nebulized	-0.43	-0.89	0.03
Nebulized	Jankelson, 1997	Nebulized	-0.20	-0.59	0.20
Nebulized	Nosedal, 1997	Nebulized	-0.11	-0.41	0.18
Nebulized			-0.42	-0.74	-0.10
Systemic	Abernethy, 2003	Systemic	-0.50	-0.78	-0.24
Systemic	Poole, 1998	Systemic	-0.47	-1.05	0.11
Systemic	Light, 1996	Systemic	-0.57	-1.62	0.48
Systemic	Eiser, 1991 (1)	Systemic	0.22	-0.28	0.72
Systemic	Eiser, 1991 (2)	Systemic	-0.26	-0.96	0.44
Systemic	Johnson, 1983	Systemic	-0.43	-0.62	-0.23
Systemic	Woodcock, 1982	Systemic	-0.28	-0.78	0.20
Systemic	Woodcock, 1981	Systemic	-0.78	-1.56	0.04
Systemic			-0.36	-0.60	-0.12
Overall			-0.38	-0.58	-0.19



# breathlessness

**Patients' perceptions about opioids after being prescribed them for breathlessness in COPD patients (n=44)**

**Semi-structured one-on-one interviews**

**3 themes**

- Small gains have a big impact**
- Hope versus reality**
- Try it!**



# breathlessness

## Patients' perceptions about opioids after being prescribed them for breathlessness in COPD patients (n=44) for 6 months

<b>0-10 numerical rating scale</b>	<b>dose</b>	<b>n</b>
Baseline	7.0 (5.0 to 8.0)	44
2 weeks	5.0 (4.0 to 7.0)      4.6 ± 1.5mg	39
2 months	5.0 (4.0 to 6.0)      8.1 ± 3.9mg	34
4-6 months	5.0 (4.0 to 6.0)      10.2± 4.3mg	31
<b>Net impact</b>	<b>-2.0 (-3.0 to 1.0) (p = 0.02)</b>	

Rocker G et al. Opioid therapy for refractory dyspnea in patients with advanced chronic obstructive pulmonary disease: patients' experiences and outcomes. CMAJ Open 2013 Jan 24;1(1):E27-36. doi: 10.9778/cmajo.20120001



# Opioid therapy

Currow et al. *J Pain Symptom Manage* 2011

D - Phase II dose ranging; Phase IV long term effectiveness / safety

P - Opioid naïve palliative care patients with breathlessness

I - Sustained release morphine 10-30mg p.o. / 24 hrs

C - none

O - 31 participant/years of data from 85 participants (up to 660 days)

For every 1.6 people you treat, one will benefit. (2.1 at 3/12)

Of responders, 92% responded at or below 20mg / 24 hours.

For every 4.5 people you treat, one will cease the medication because of immediately reversible side-effects.

No evidence of tachyphylaxis

No hospitalisations for respiratory depression nor obtundation



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# Breathlessness – opioid titration

Currow et al. *J Pain Symptom Manage* 2011

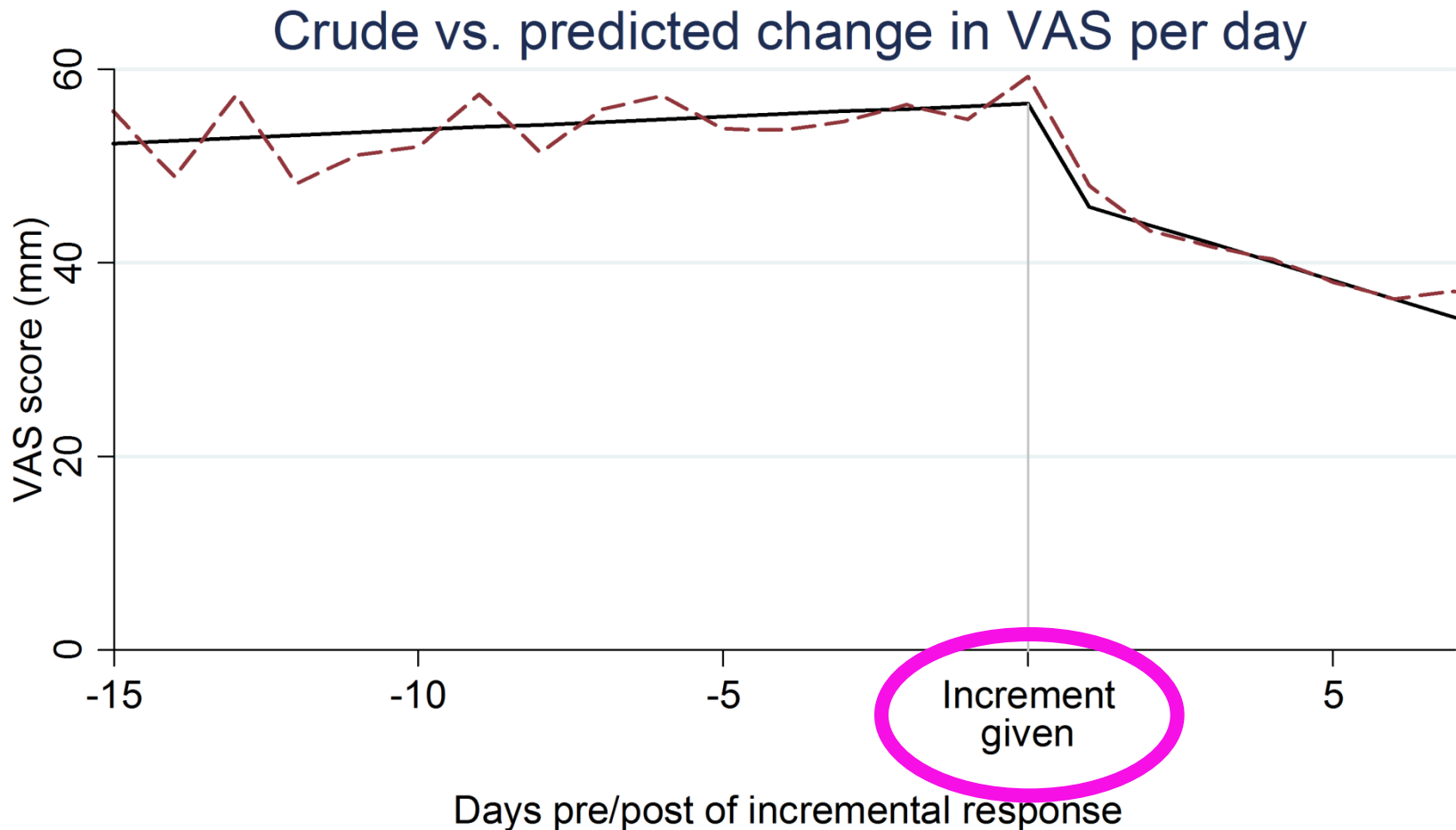
17 people      - 13 who were titrated to 20mg / day; and  
                    - 4 who were titrated to 30mg / day.

8 males; median age 82 (63-88); median AKPS 60 (50-80)

9 people with chronic obstructive pulmonary disease (COPD)



# Changes in VAS when people respond to titration of sustained release morphine for refractory breathlessness



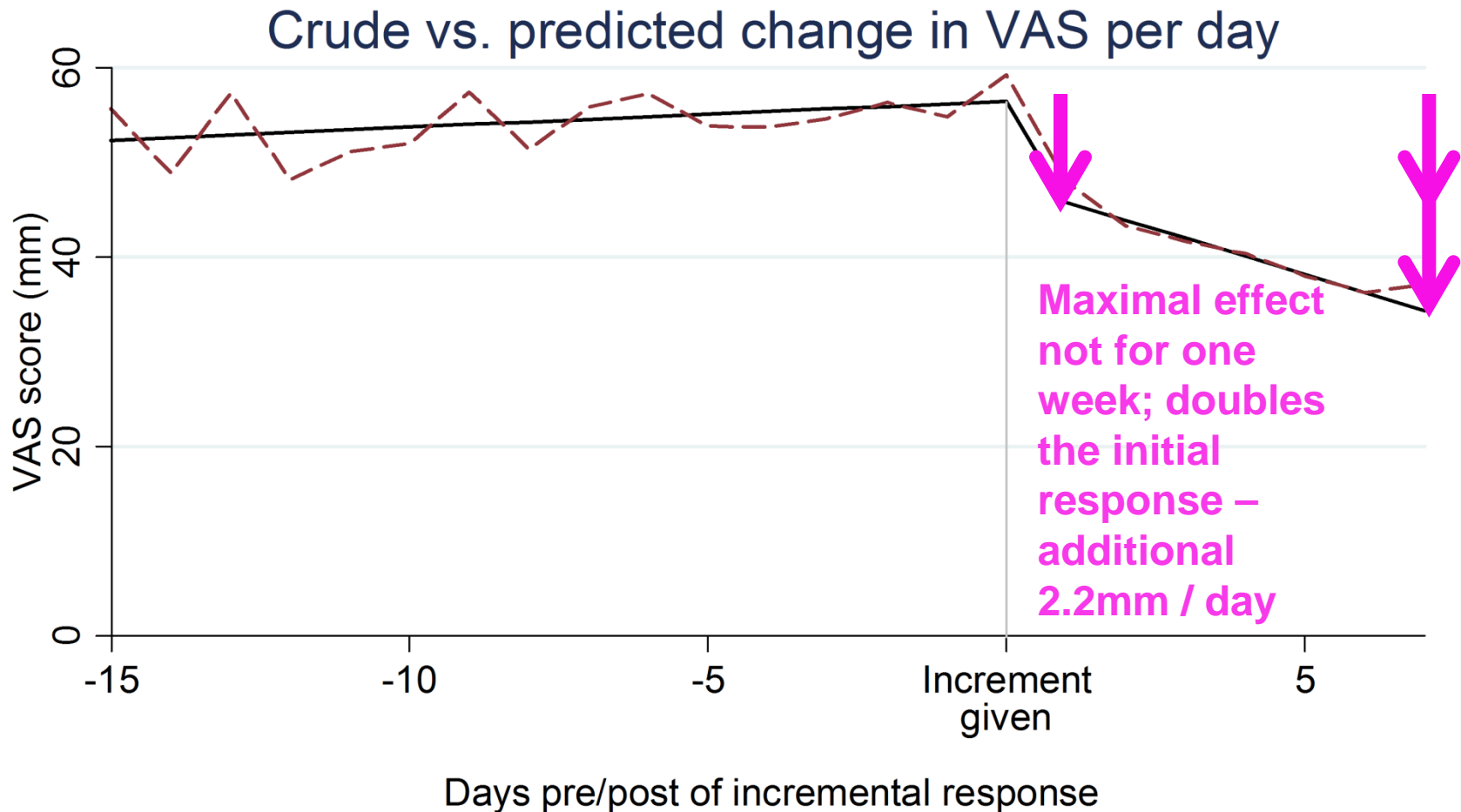
Reduction (95% CI) in VAS on the first day after last dose increment = 10.9 (7.0, 14.7),  $p < 0.001$ .

Subsequent reduction (95% CI) in VAS/day after last dose increment = 2.2 (1.3, 3.2),  $p < 0.001$ .

13 subjects responded at 20mg, 4 subjects responded at 30mg



# Changes in VAS when people respond to titration of sustained release morphine for refractory breathlessness

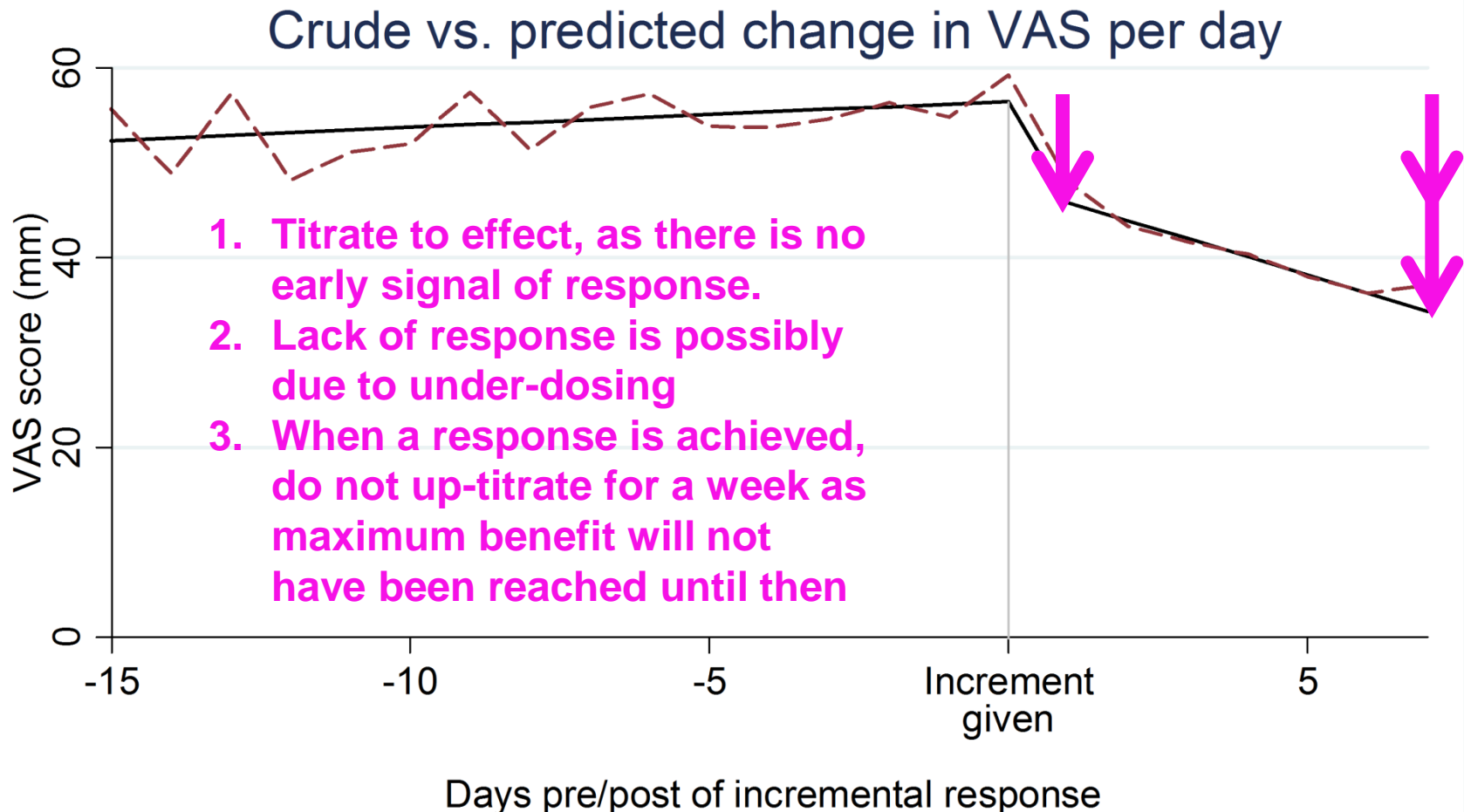


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breathlessness

## Opioid therapy



Johnson et al. 2013. Eur Rep J

### **Predictors of response to opioid therapy.**

In the final regression model:

**higher baseline breathlessness intensity** scores strongly predicted absolute and relative response ( $p < 0.001$ ); and

**younger age** also predicted relative response ( $p = 0.025$ ).;

Some evidence supported the descriptor "not enough air", but was not statistically significant ( $p = 0.052$ ).

Functional status and underlying aetiology did NOT predict response

breathlessness

## Opioid therapy



Currow DC et al 2015. BMJ Open [in press]

- D - Cross-sectional, convenience sample. Exploratory study.
- P - 1672 people on opioids for pain; 17 centres; 11 countries
- I - On morphine (n=588) OR fentanyl (=405) OR oxycodone (n=429)
- O - Breathlessness scores when evaluated against 112 candidate single nucleotide polymorphisms (SNP) on 25 genes thought to influence opioid receptors, signalling or pain modulation.

breathlessness

## Opioid therapy



Currow DC et al 2015. BMJ Open [in press]

Results – In the multivariable model (adjusted for available confounders and clustering over country) one SNP remained significant – rs7103572 (HTR3B gene).

People with this variant were three times *more* likely to have more intense breathlessness despite being on opioids.

# Opioids in a population qualifying for long term oxygen therapy

Ekström MP et al. *BMJ* 2014

D – Prospectively collected data in a national longitudinal consecutive cohort in Sweden using the *Swedevox* database.

P – 2249 people with COPD 2005-2009: 59% women

I – 535 (24%) on opioids; 509 (23%) on benzodiazepines; and 200 (9%) on both.

C – The rest of the cohort

O – No difference in mortality nor hospital admissions with low dose opioids ( $\leq 30$ mg oral morphine equivalent daily), nor benzodiazepines, nor the combination, even when controlling for CO<sub>2</sub>.



Adjusted hazard ratios with 95% confidence intervals.

***n = 2,249 ; 1,681 had admissions to hospital; 1,129 died  
535 taking benzodiazepines (24%); 509 taking opioids  
(23%); 200 (9%) taking both***

Subgroup

Admission

Mortality

**Benzodiazepines**

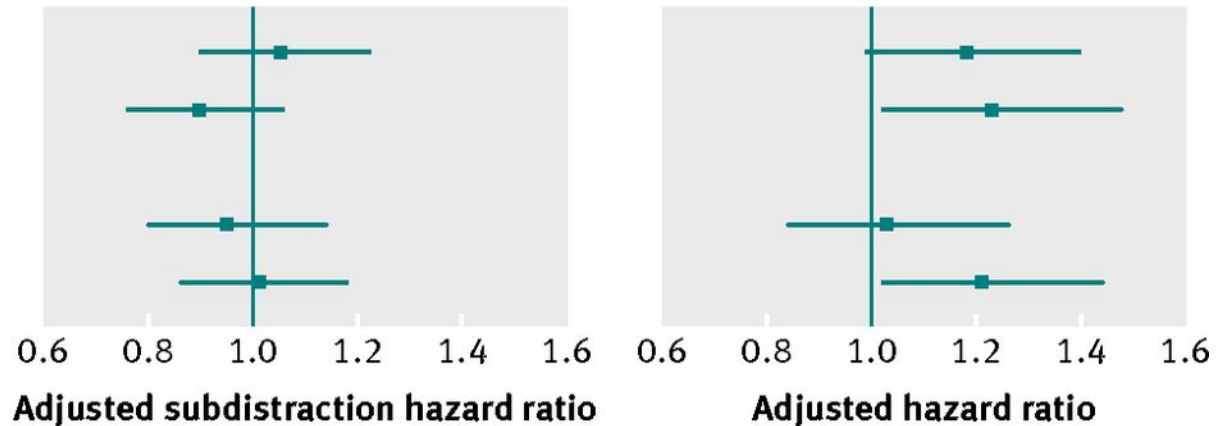
Low dose ( $\leq 0.3$  DDD/day)

High dose ( $> 0.3$  DDD/day)

**Opioids**

Low dose ( $\leq 0.3$  DDD/day)

High dose ( $> 0.3$  DDD/day)



Adjusted hazard ratios with 95% confidence intervals. Rates of hospital admission rates adjusted for WHO performance status, number of previous admissions, number of cardiovascular diagnoses, diabetes mellitus, osteoporosis, and treatment with oral glucocorticoids. Mortality adjusted for age, sex, PaO<sub>2</sub> air, PaCO<sub>2</sub> air, WHO performance status, BMI, anaemia, number of cardiovascular diagnoses, renal failure, and oral glucocorticoids. DDD=defined daily dose

Ekström M P et al. BMJ 2014;348:bmj.g445



# Breathlessness

## **Beliefs about prescribing opioids**

**– family physicians (n=10)**

## **In-depth interviews**

**- discomfort prescribing opioids**

## **Barriers included:**

**- insufficient knowledge;**

**- lack of education; and**

**- fear of censure.**

Young J et al. Using opioids to treat dyspnea in advanced COPD: attitudes and experience of family physicians and respiratory therapists. Can Fam Physician 2012 Jul;58(7):e401-7.





# Breathlessness

## **Beliefs about prescribing opioids**

**– physicians (n=28)**

## **Semi-structured interviews**

**Most physicians were reluctant to prescribe opioids for refractory dyspnea, describing:**

- a lack of related knowledge and experience;**
- fears related to the potential adverse effects; and**
- fears of legal censure.**

Rocker G et al. Perspectives of patients, family caregivers and physicians about the use of opioids for refractory dyspnea in advanced chronic obstructive pulmonary disease. *CMAJ* 2012 Jun 12;184(9):E497-504.



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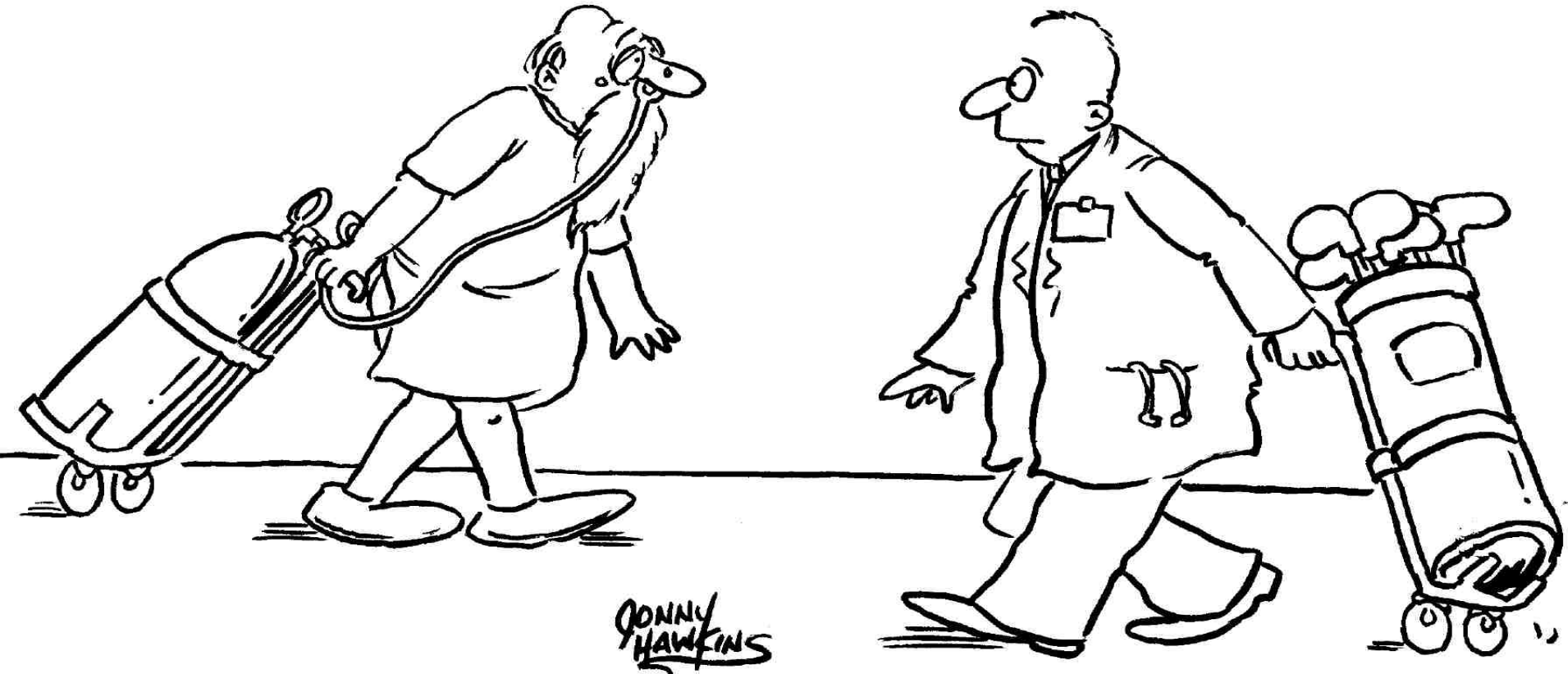
3. Opioids

4. Oxygen



POST  
OP  
←

D HALL  
→



DONNY  
HAWKINS

# Oxygen therapy

- Uronis et al *Cochrane database of systematic reviews* 2011

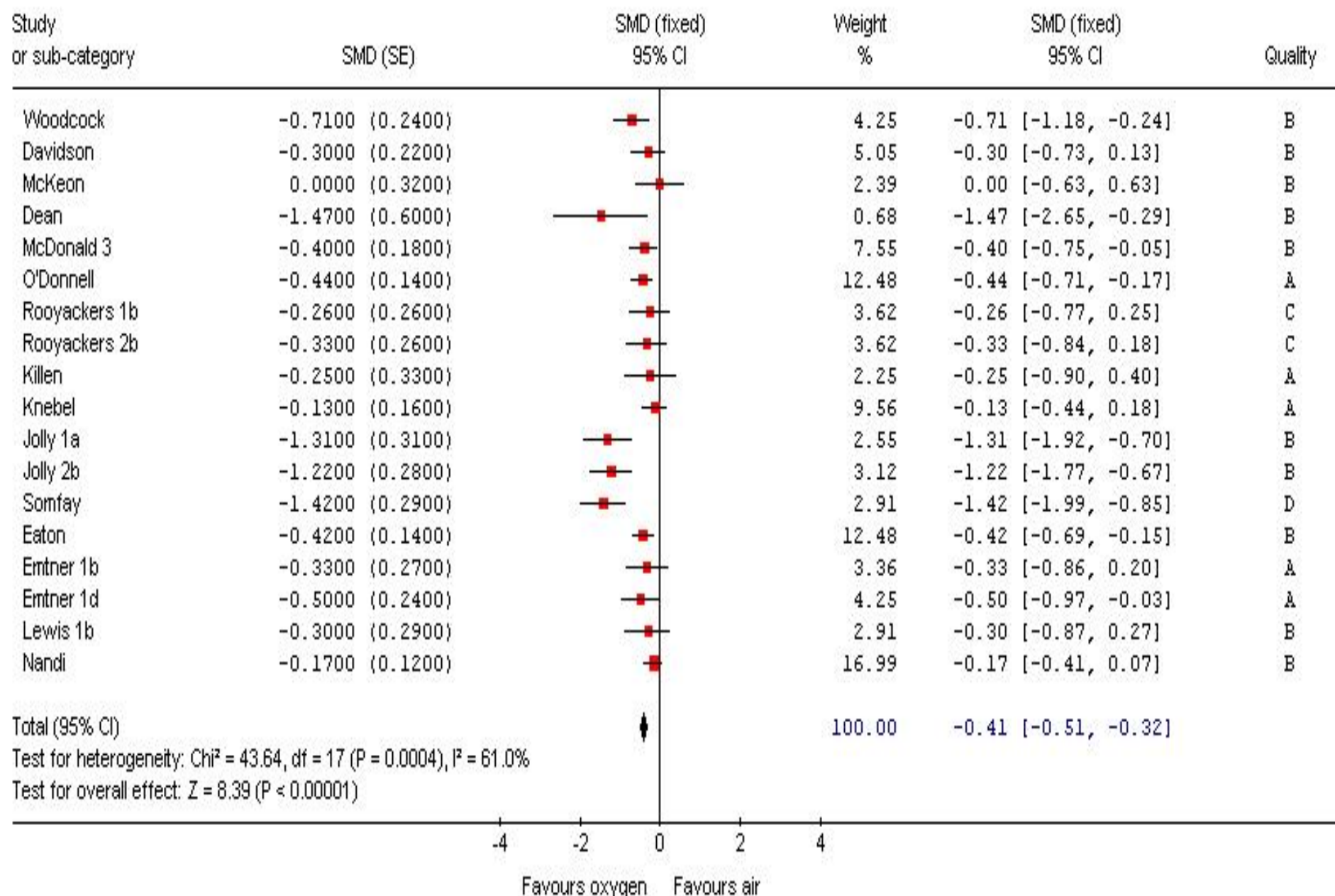
Mean study quality score 2.9

- D - Cochrane review of symptomatic benefit of oxygen in people with COPD of 18 studies and 321 participants
- P - People with COPD (mean FEV<sub>1</sub> 0.9l) who do NOT qualify for domiciliary O<sub>2</sub>
- 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 had reduced breathlessness in the intervention arm



Review: Palliative oxygen therapy for dyspnea in COPD with mild or no hypoxia  
 Comparison: 01 Oxygen vs air  
 Outcome: 01 Breathlessness



# Oxygen therapy

Patients define net clinical effect discerningly  
Sub-study of the Oh to (O<sub>2</sub>) Breathe study

38/110 participants described oxygen therapy as 'not burdensome'

55/110 derived insufficient benefit to request further oxygen.

*Patients not deriving benefit are unlikely to continue therapy that entails burden but provides no symptomatic relief*

*The role of n=1 studies needs to be considered*



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# **Symptom control in interstitial lung disease**

## **Bottom line**

- Significant symptom burden**
- Evidence-based options are limited, but available**
- Much more research needs to be done in this area**

