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- **Refractory dyspnea:
Treatment of reversible causes have
been, or are being, optimised**
- **Clinical goal of care is focused on
symptomatic relief without causing
(unacceptable) reductions in function
or wellbeing**

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Do we still see breathlessness in terms of tachypnoea (and hence a *clinical sign*) rather than, at times, a *distressing symptom* to be directly addressed?

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...the *sensation*

- **Refractory dyspnea:**
 - Stimulus
 - Transmission
 - *Meaning (Ever been really breathless?)*
 - Response

Together, this generates the sensation – with wide inter-person variation in perception with the same levels of objective pathology

Nosedá et al. Eur Resp J 1992.

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...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

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Pharmacology of breathlessness

No medication registered with EMEA / FDA / PMDA/ TGA for the treatment of symptomatic refractory or intractable breathlessness.

Evidence supports efficacy and safety of opioids for symptomatic breathlessness

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New guidelines for the symptomatic treatment of dyspnoea – American Thoracic Society, 2012

- **1999 ‘Despite the beneficial effects of opiates , for acute dyspnoea there is insufficient evidence to recommend their regular use in the longterm management of dyspnea.’**
- **2012 ‘Short term administration of opioids reduces breathlessness in patients with a variety of conditions...’**

Anon. ATS statement. Am J Respir Crit Care Med 1999;159:321-340
Parshall MB et al. Am J Respir Crit Care Med 2012;185(4):435-452.



- 1. Generating breathlessness**
- 2. Imaging breathlessness**
- 3. Opioids and breathlessness**



- 1. Generating breathlessness**
2. Imaging breathlessness
3. Opioids and breathlessness



1. **Generating breathlessness**

- a. **In the laboratory**
- b. **clinically**

2. **Imaging breathlessness**

3. **Opioids and breathlessness**



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Basic science

Underlying aetiology > Descriptors > targeted therapy

breath-holding;

CO₂ inhalation;

inhalation of CO₂, with ventilation voluntarily targeted below the level dictated by chemical drive;

breathing with a resistive load;

breathing with an elastic load;

voluntary elevation of functional residual capacity;

voluntary limitation of tidal volume; and

exercise.

Simon P et al. Am Rev Respir Dis 1989



My breath does not go all the way out

My breathing requires effort

I feel that I am smothering

I feel a hunger for more air

My breathing is heavy

I cannot take a deep breath

I feel out of breath

My chest feels tight

My breathing requires more work

I feel that I am suffocating

I feel that my breath stops

I am gasping for breath

My chest is constricted

I feel that my breathing is rapid

My breathing is shallow

I feel that I am breathing more

I cannot get enough air

My breath does not go all the way out

My breathing requires more concentration

Simon PM et al. Am Rev Resp Dis 1989;140:1021-1027.



3 'dimensions of the experience of breathing discomfort'

1. Depth and frequency of breathing

Physiology – tidal volume and respiratory rate

'I am breathing more' 'My chest is constricted'

2. Perceived urge or need to breathe

Physiology – increased respiratory drive

Pathophysiology – exercise, congestive heart failure, pregnancy

'I feel hunger for air' 'My breathing is shallow'

3. Difficulty breathing and phase of respiration

Physiology – inspiratory or expiratory effort

Harver A et al. Chest 2000;118:679-690.



...the *sensation*

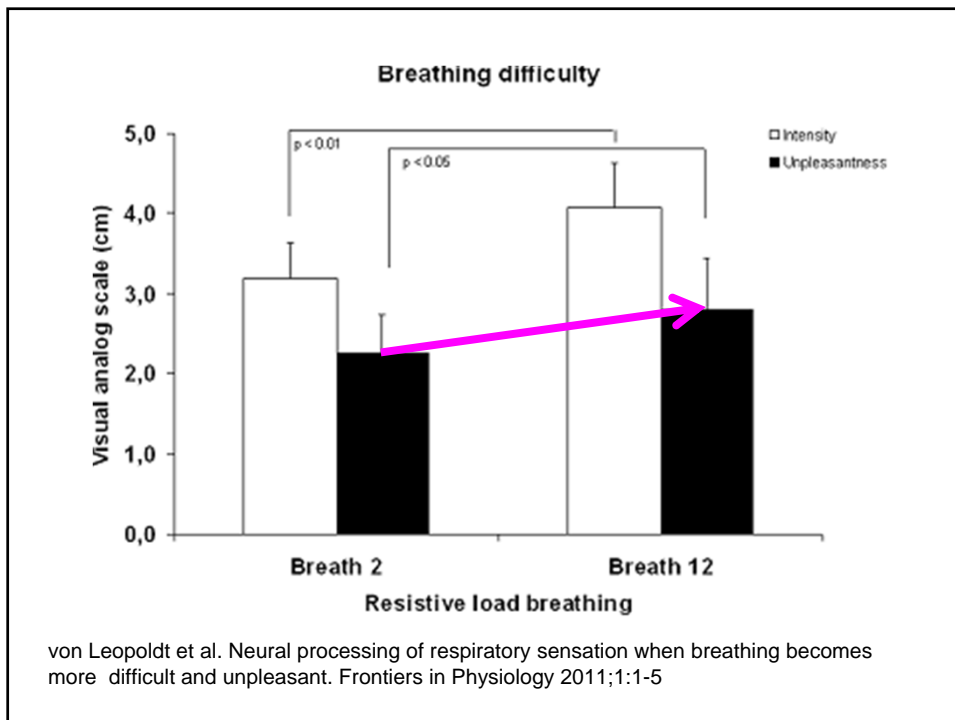
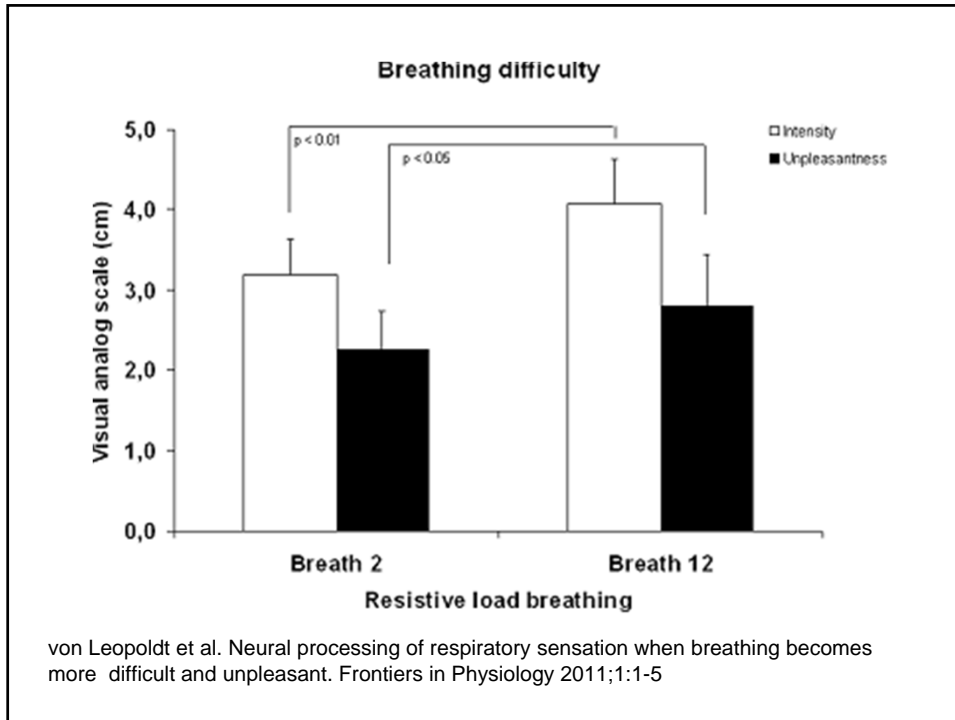
Intensity of breathlessness is probably what we ask patients

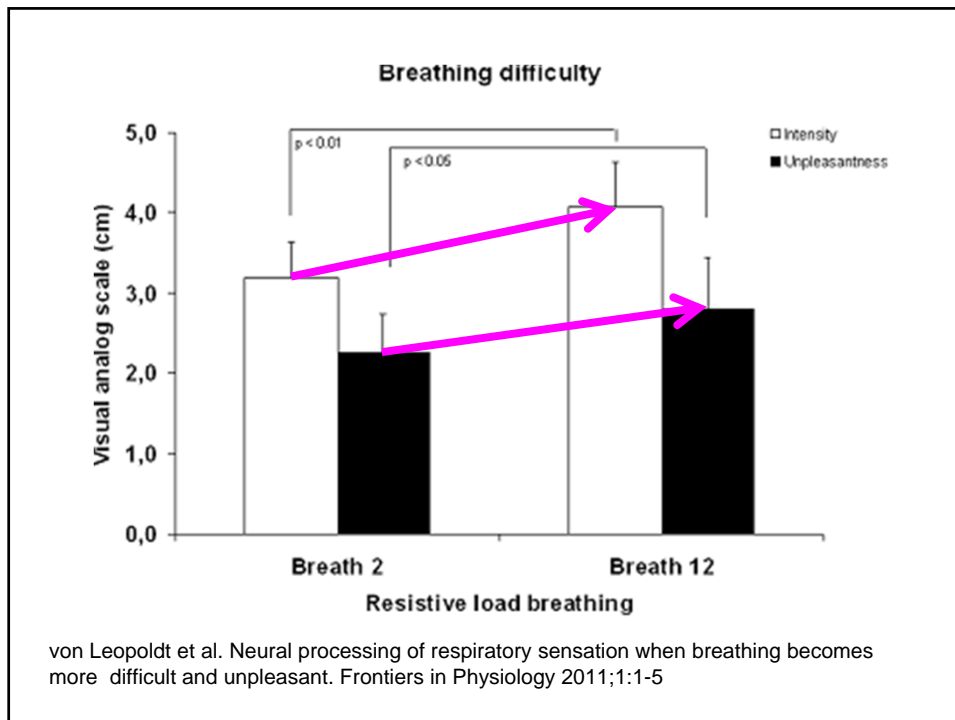
But there is good evidence that the *intensity* may be less important than *how unpleasant the sensation is*

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

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







1. Generating breathlessness

- a. In the laboratory
- b. clinically

2. Imaging breathlessness

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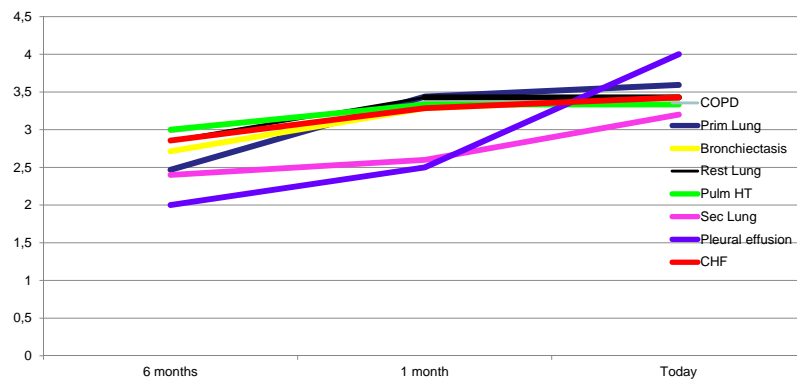


Do dyspnoea trajectories (intensity over time) differ by underlying aetiology?



Basic science - trajectories of breathlessness over time depending on underlying aetiology; n = 210

mMRC



Why is there a need to look at the individual components that contribute to the sensation of dyspnoea?

Pathophysiology >

Sensation(s) experienced >

**Best possible intervention(s)
to reduce the sensation**



Measuring dyspnoea

Severity (intensity)

Affective component (unpleasantness)

**Exercise induced evidence for
different gradients of response**

**fMRI evidence of different areas of
cerebral stimulation**



Clinical science

n=91, 47m, FEV₁ 54% predicted

In people with COPD, affective descriptors (frightening, awful, worrying) correlated with BODE* and functional status, whereas intensity did not.

(body mass index, airflow obstruction, dyspnoea, exercise tolerance)
Williams M et al. Chest 2010



Clinical science

Comparison of people with COPD with healthy age appropriate controls

Only individuals with COPD used the descriptors, “smothering,” “constricted,” “suffocating,” and “cannot get enough air.”

Williams M et al. Chest 2008



...the *sensation*

Intensity of breathlessness is probably what we are asking when we ask patients about breathlessness

But there is good evidence that the *intensity* may be less important than *how unpleasant the sensation is* and how it affects the person emotionally (different slopes as exercise intensity increases)

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

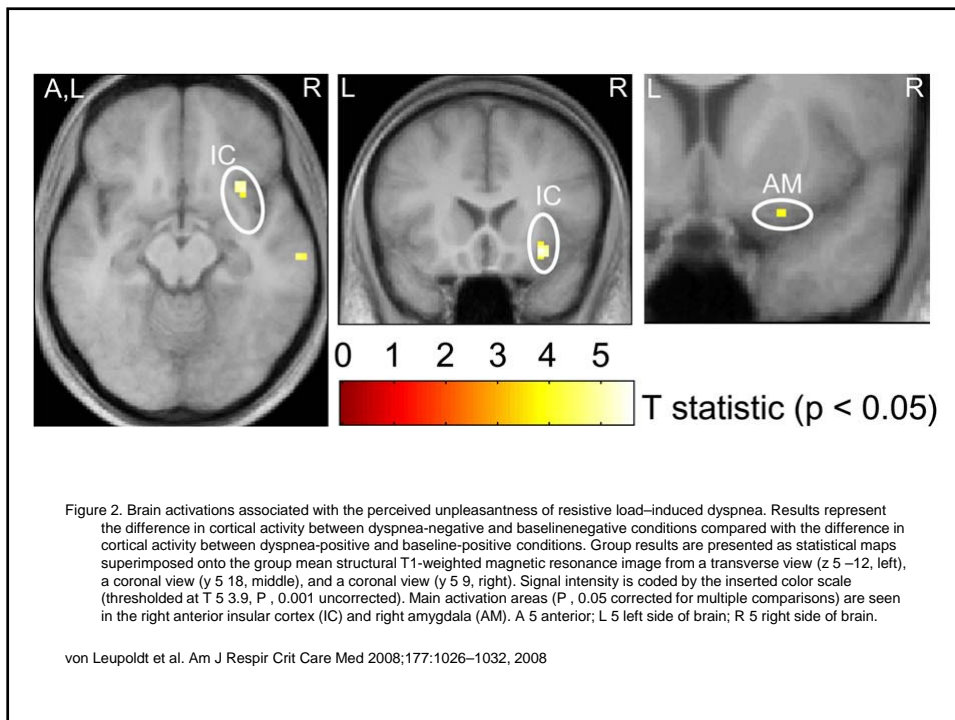
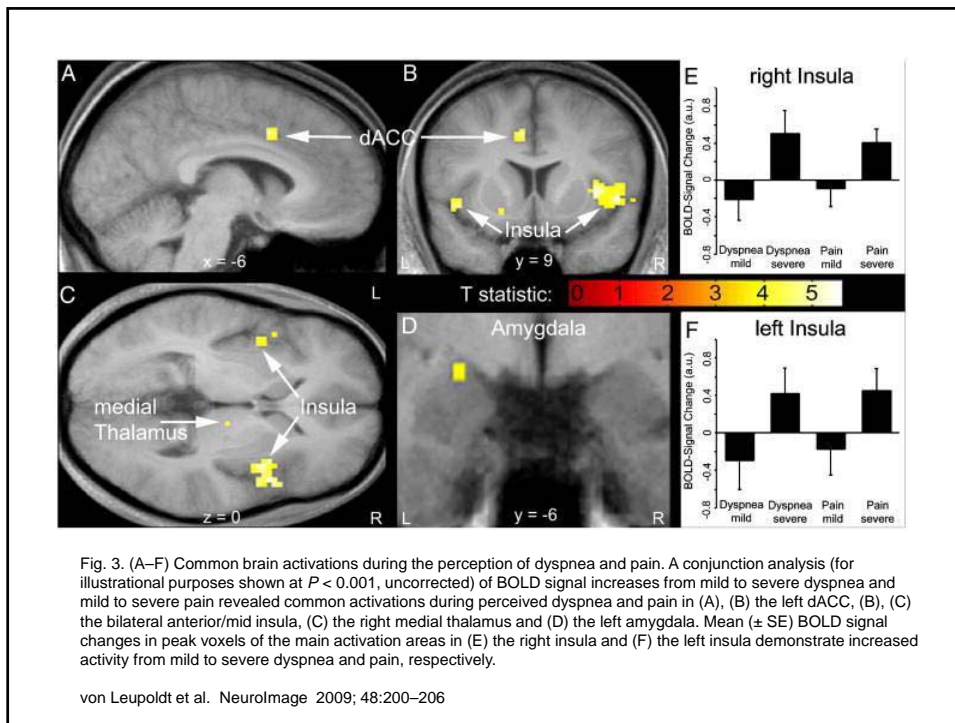
Lansing et al, Resp Physiol Neurobiol 2009 , von Leupoldt et al. Chest 2005, Williams et al. Chest 2010

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Dyspnoea 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



Dyspnoea Opioid therapy

- Gifford AH et al *COPD* 2011

- D - Double blind, randomised crossover
- P - 14 people with moderate to severe COPD
- I - Naloxone 10mg i.v. before resistive load breathing (to get unpleasantness and / or intensity to >50/100mm)
- C - Normal saline
- O - Intensity and unpleasantness both worse in the naloxone arm

Results – In the naloxone arm, significantly:

- Harder to breathe

No differences in the physiological measures in either arm



Dyspnoea Opioid therapy

- Banzett RB et al *Am J Respir Crit Care Med* 2011

- D - Double blind, randomised crossover
- P - 6 healthy volunteers
- I - Morphine 0.07 mg/kg with a 60% breathing discomfort score
- C - Normal saline
- O - Perceptual response (air hunger) and ventilatory response

Results – In the morphine arm, significantly:

- Reduced discomfort of breathing (65%)
- Reduced ventilation (28%)



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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 dyspnoea
- I - Sustained release morphine 10mg / 24 hours titrated until response up to 30mg / 24 hrs
- C - none
- O - 31 participant/years of data from 85 participants (1-660 days)

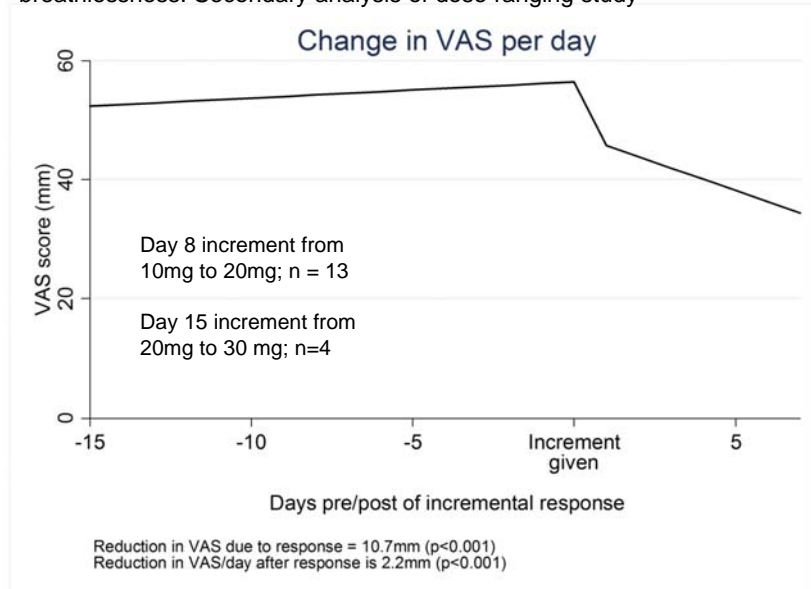
Number needed to treat 1.6 (2.1 at 3/12)

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

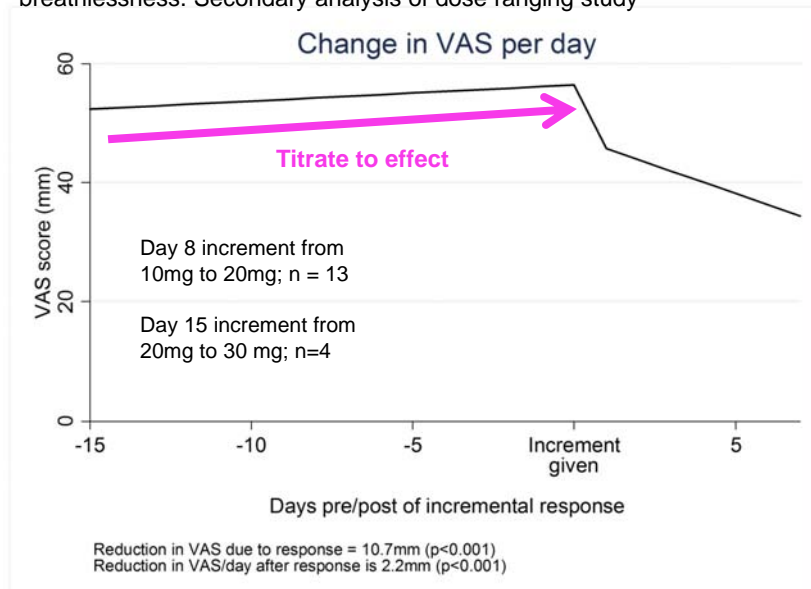
Number needed to harm 4.5



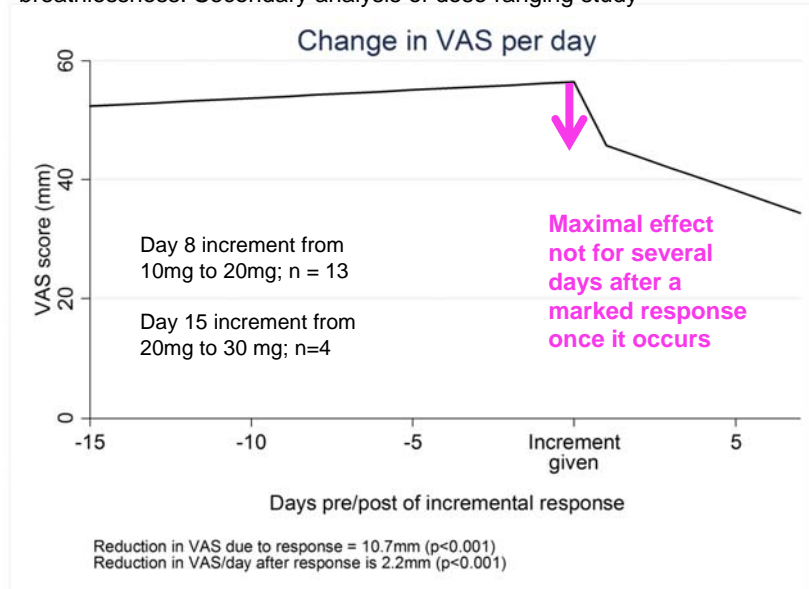
Changes in VAS in people who have responded to dose titration on sustained release morphine for refractory breathlessness. Secondary analysis of dose ranging study



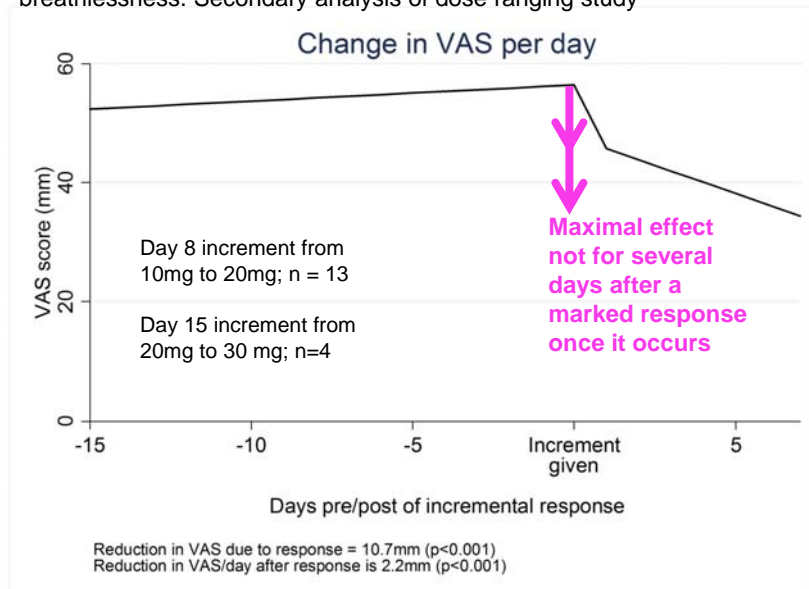
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**Minimum clinically important
difference in dyspnoea intensity**

**In the acute care setting – a 2 point
difference on a 0-10 numerical rating
scale may be required for patients to
feel that there is any difference to the
relief of their breathlessness**

Ander DS et al. Congest Heart Failure 2004;10(4):188-191. Karras DJ et al
Acad Emerg Med 2000;7(4):327-334, Ries AL. COPD 2005;2(1):105-110



**Minimum clinically important
difference in dyspnoea intensity**

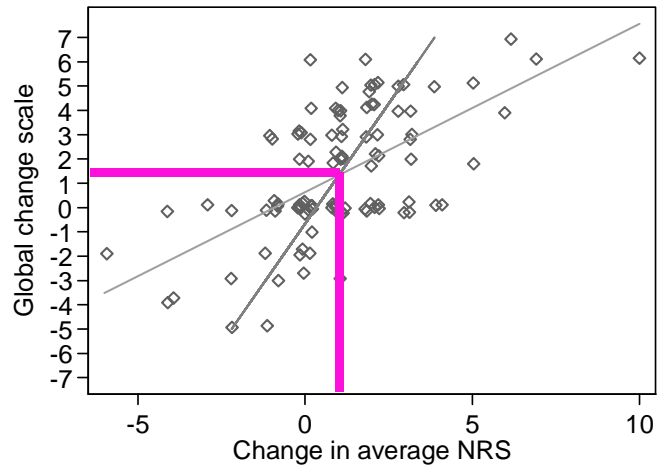
**In the chronic setting, it is thought that
the threshold for patient-defined
differences may 1 on a 0-10 numerical
rating scale.**

Booth S. Palliat Med 2006;20(3):219-220

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Two reciprocal regression lines (average NRS for breathlessness intensity) compared to a single point in time global impression of change in chronic heart failure



Thanks to Dr Miriam Johnson of Hull York Medical School for this graph



Generating stronger evidence about central mechanisms in breathlessness with interesting laboratory and clinical correlates that have direct impact on research and on clinical practice

