



Palliating chronic breathlessness

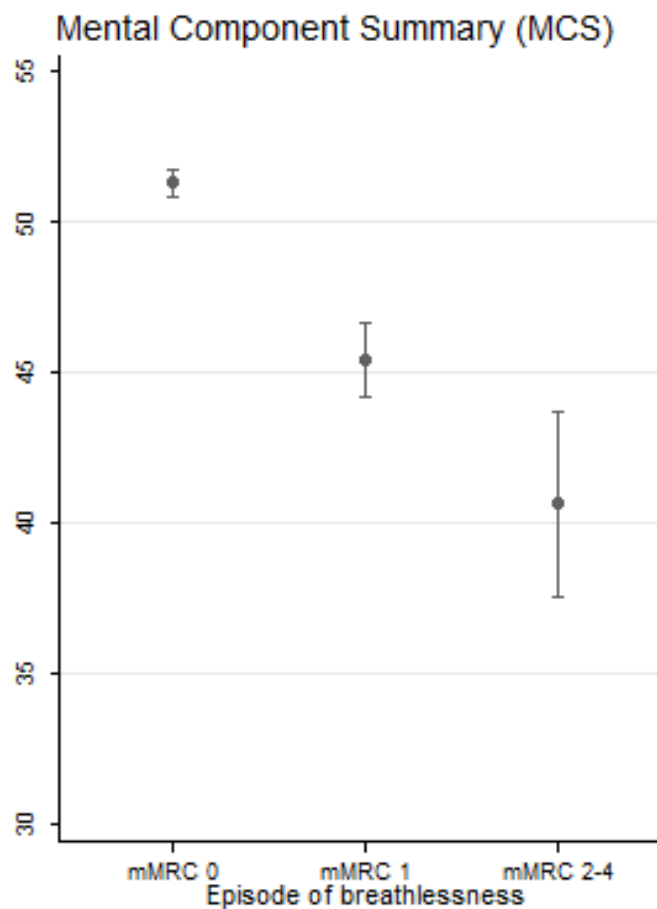
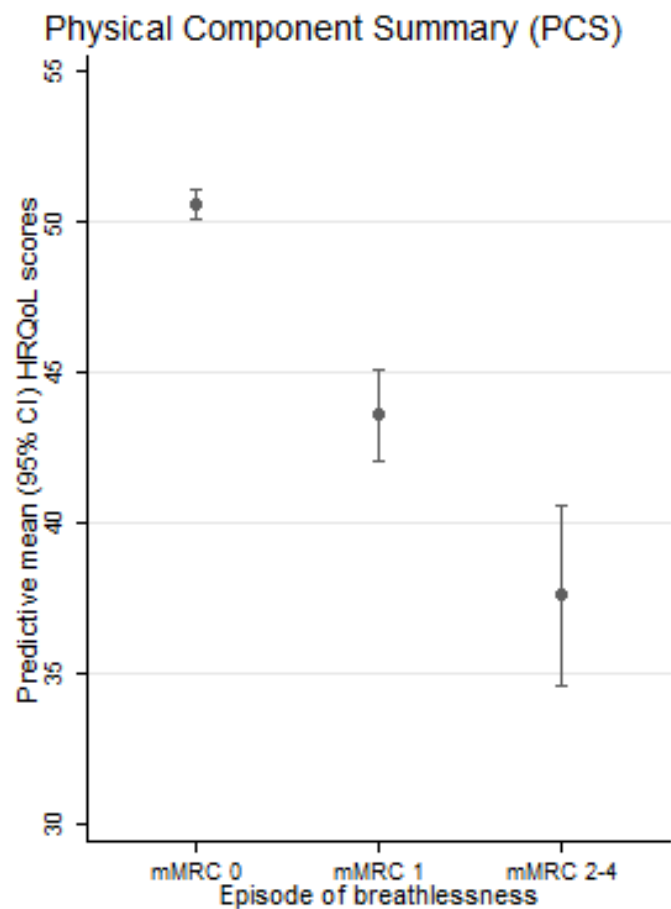
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Content

- Chronic breathlessness - definition
- Management
 - Non-pharmacological
 - Pharmacological
- Any questions?

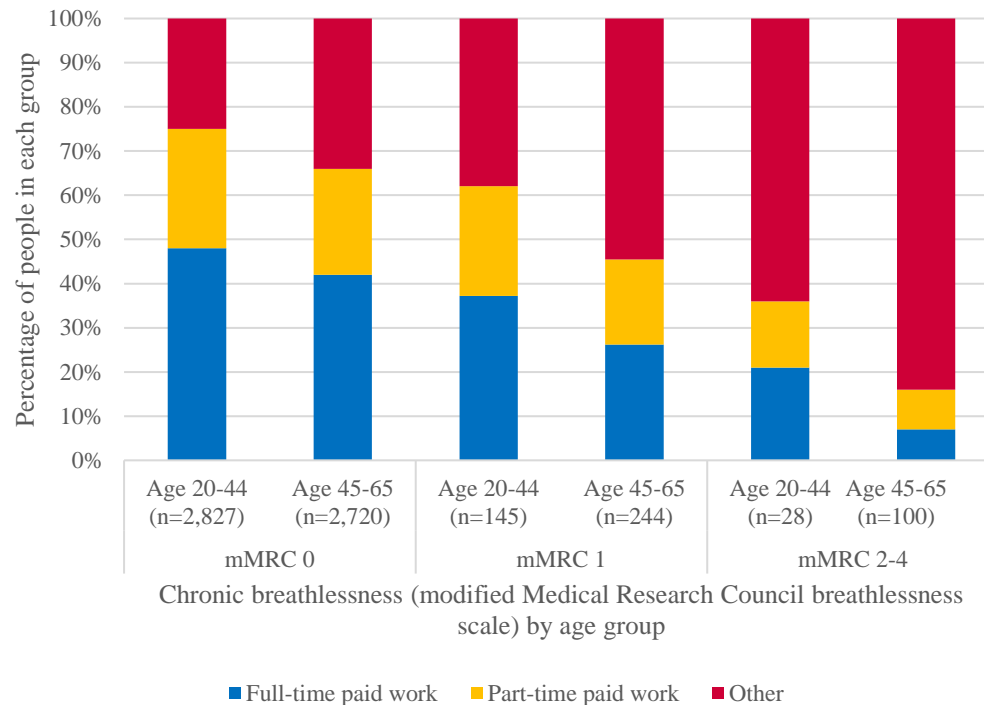
Quality of life and the impact of chronic breathlessness (whole adult population)



Currow D et al. Thorax
2017. 72; 1151-1153

The impacts of persisting breathlessness on workforce participation in people of working age

Percentage of people participating in the paid workforce by level of chronic breathlessness (n=6064) from a randomly selected cross-section of the population aged 20-65.



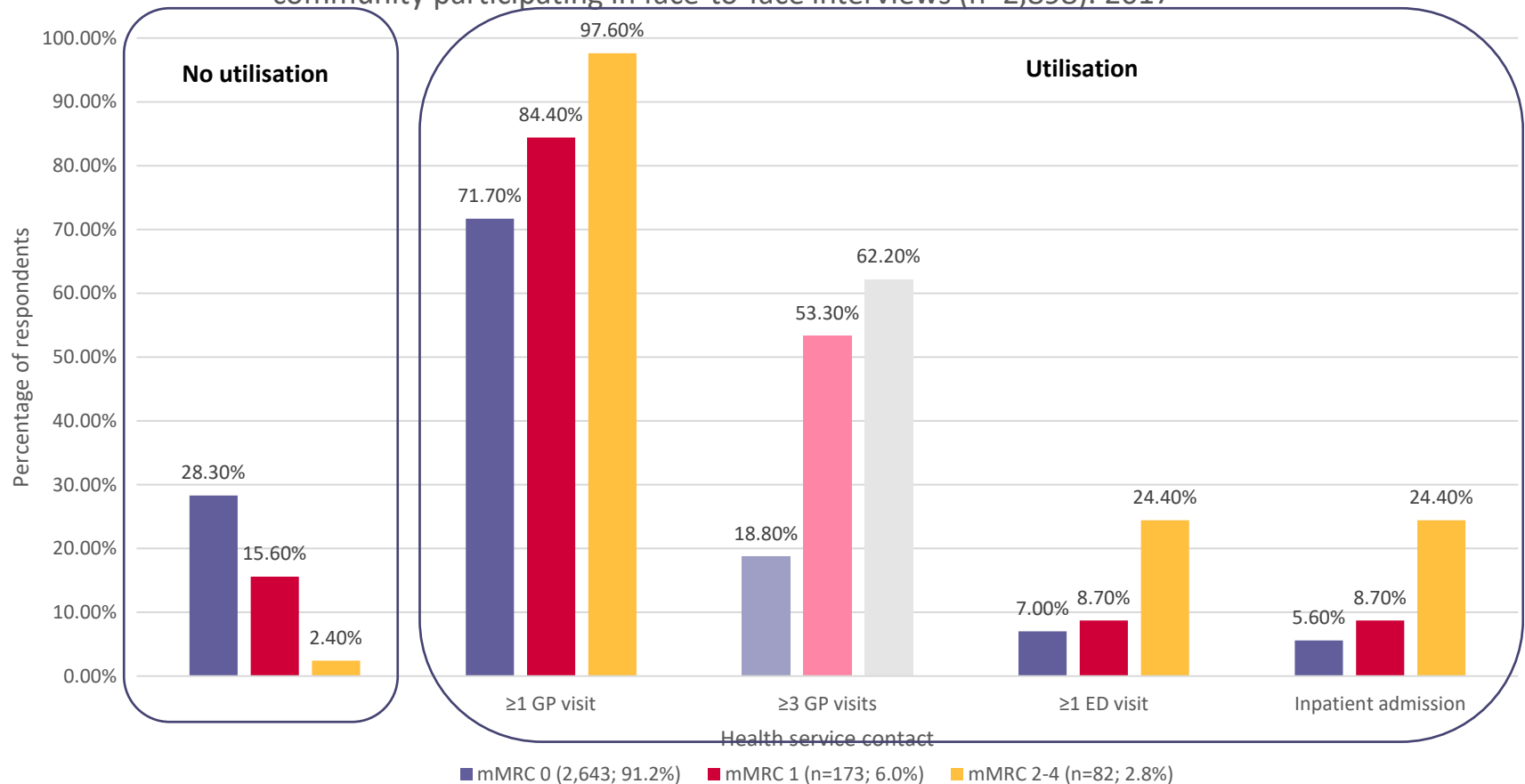
Face-to-face interviews in people's own home.

Data from three years ('06, '15, '17).

Analysis limited to people of working age.

Persisting breathlessness and health service utilisation

Health service contact by level of persisting breathlessness in a random sample of the community participating in face-to-face interviews (n=2,898). 2017



mMRC – modified Medical Research Council breathlessness scale; GP – general practitioner; ED – emergency department

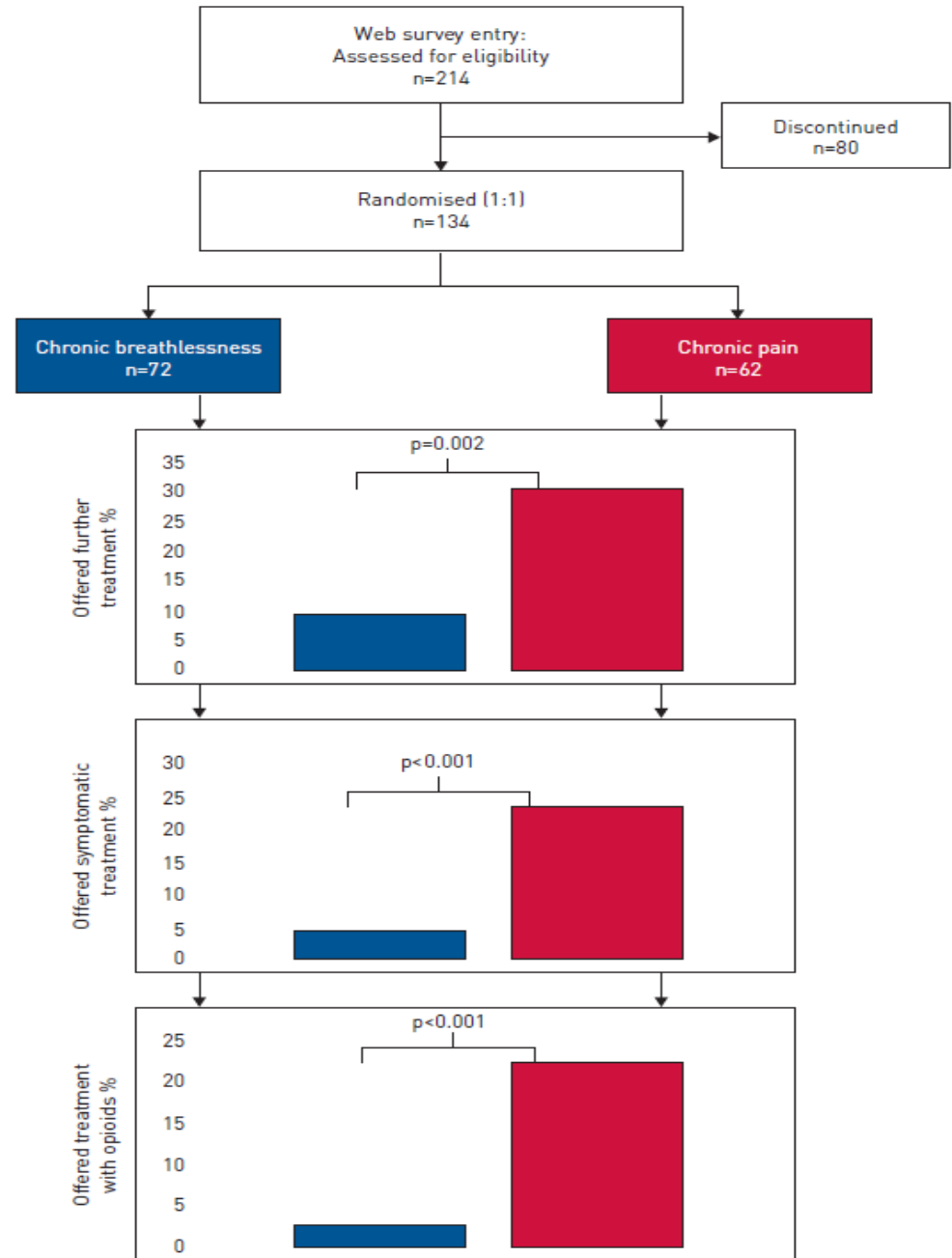
Not noticed...

Ahmadi Z et al ERJ 2018

- 59 years old, severe COPD former smoker,
- + triple inhalation therapy, 'flu/pneumococcus vaccine
- individualised pulmonary rehabilitation
- At follow-up, severe ["breathlessness" or "pain"] that markedly restricted daily activities, unchanged for at least three months.
- Taking paracetamol/ NSAID allergy

Questions to respiratory physicians

1. Needs further treatment?
2. What type of treatment?



Management of chronic breathlessness

Chronic is different: central processing

- The brain creates expectations and beliefs (psychological “priors”) based on previous experience which influence incoming breathlessness sensations . Faull O et al Cortex 2017
- People living with chronic breathlessness process the sensation of breathlessness involving the frontal association cortex; in the context of memory and fear associated with past experiences. Healthy volunteers do not. Herigstad M et al Chest 2015
- Interventions such as pulmonary rehabilitation, which aim to educate and change such beliefs, also show corresponding reduction in fMRI frontal association cortex activity. Herigstad M et al Eur Respir J 2017
- Opioids suppress conditioned anticipatory brain responses to breathlessness Hayen A, et al Neuroimage 2017

Managing breathlessness: general principles - a *complex intervention*

1. Non pharmacological measures
2. Morphine
3. Oxygen - not for palliation of breathlessness
4. Other drugs e.g. antidepressants
5. Manage other symptoms
6. Remember the carers!

Evidence based – complex interventions

- **Pulmonary rehabilitation**

- McCarthy B et al. Cochrane Database of Systematic Reviews 2015, Issue 2. Art. No.: CD003793.
- Spruit MA et al. Am J Respir Crit Care Med 2013 Oct 15;188(8):e13-e64.

- **Cardiac rehabilitation**

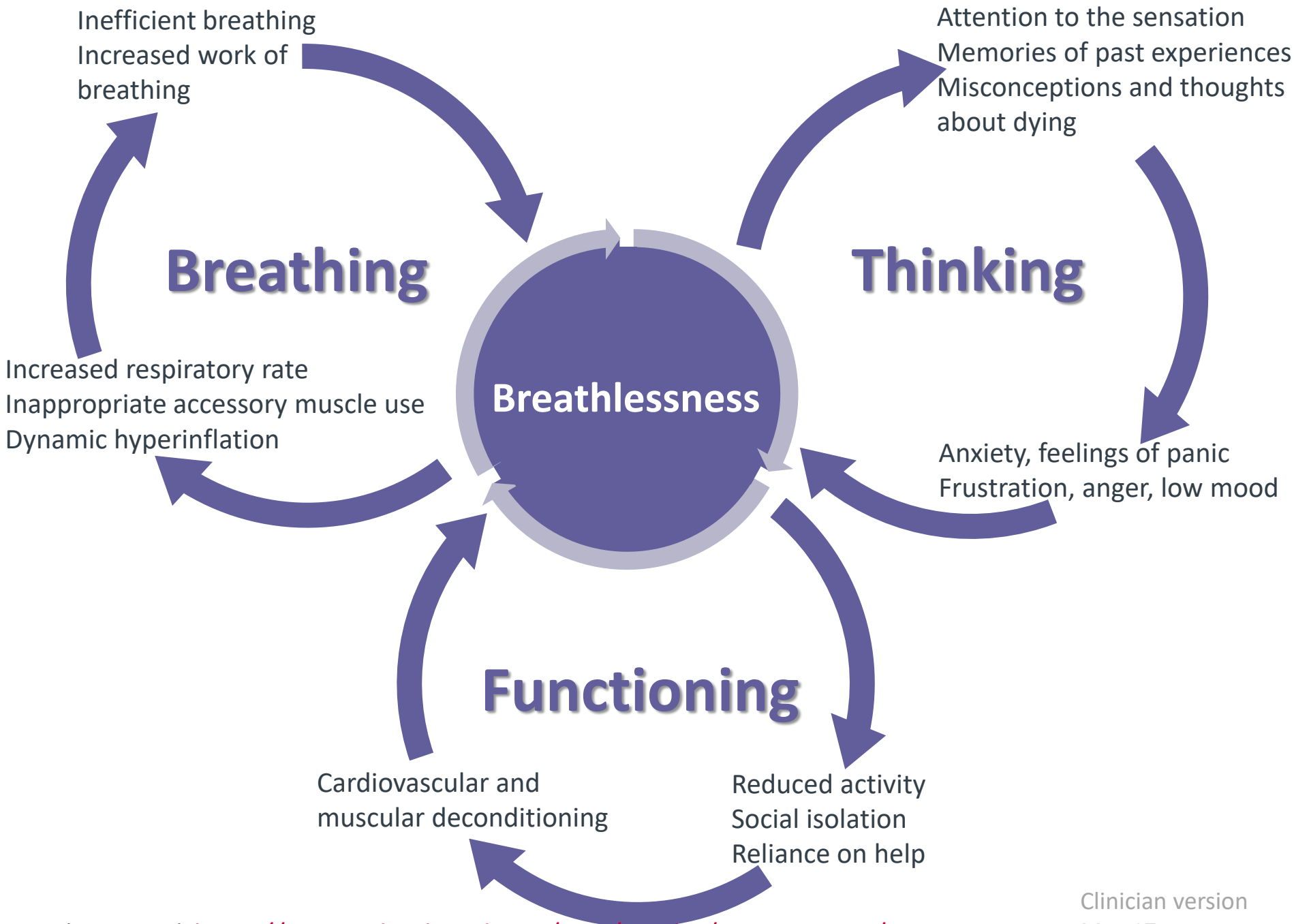
- O'Connor CM et al. JAMA 2009; 301(14):1439-1450
- McMurray JJ et al. Eur J Heart Fail 2012; 14(8):803-869

- **Generic rehabilitation**

- Evans RA et al. Respir Med 2010 Oct;104(10):1473-81

- **Breathlessness intervention services**

- Bausewein C et al Chron Resp Dis 2018, 15 (1): 48-59



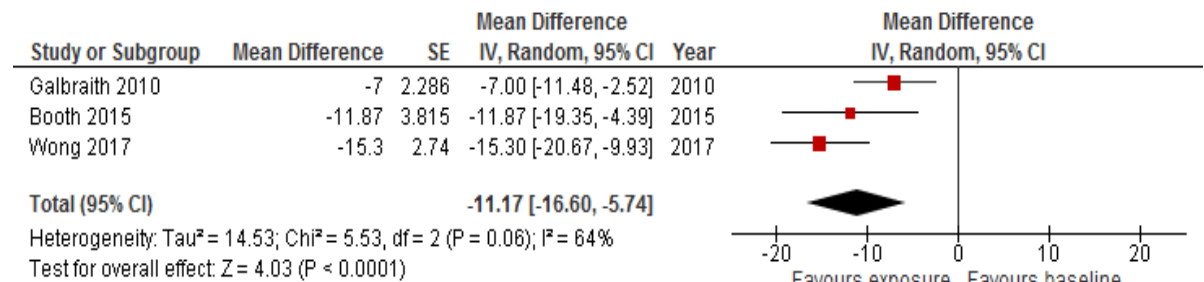
BREATHING: Airflow relieves chronic breathlessness in people with advanced disease: an exploratory systematic review and meta-analyses.

Swan F et al 2019 *Palliative Medicine*

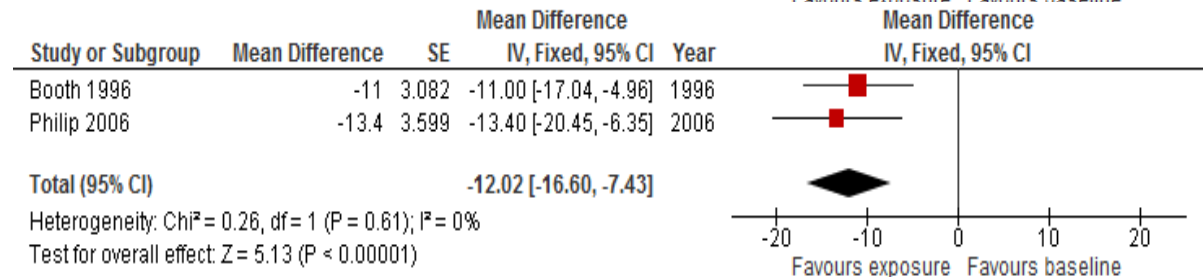
Results

16/78 studies (n=929)
11 RCTs oxygen vs medical air,
4 RCTs of fan vs control
1 fan cohort study.

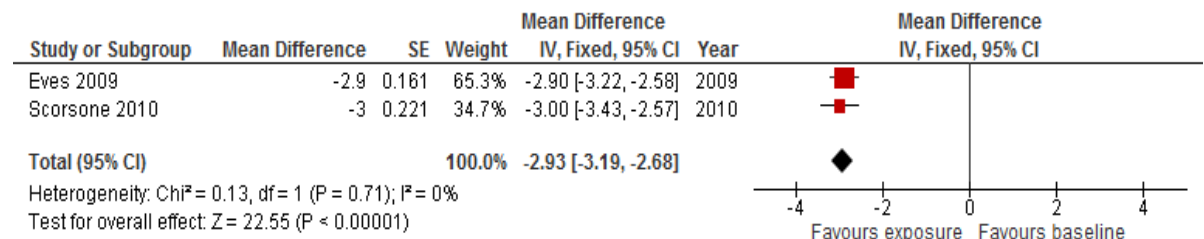
1. Fan at rest (variety of diagnoses) –



2. Airflow delivered as cylinder medical air at rest (advanced cancer)



3. Airflow delivered as cylinder medical air during a constant load exercise test (COPD completing pulmonary rehabilitation)



Breathing

Hand-held fan

- Mixed methods analysis of pooled qualitative data (n=133): 82% perceived some/substantial benefit (Luckett T *et al* 2017)
- Used as part of a complex intervention – no further trials of the individual fan component needed (Johnson MJ *et al* J Pain & Symptom Manage 2016)

Well I used to use Ventolin up to 30 times a day and I don't use it at all now...

I have a much quicker recovery than I used to...

The best things were that it worked, it had a positive effect on my condition. .. now I've resumed cooking...

THINKING

- Understand triggers, context and meaning of breathlessness
- **Crisis plans.** (Mularski RA et al. An official American Thoracic Society workshop report: assessment and palliative management of dyspnea crisis Ann Am Thorac Soc. 2013)
- Anxiety/panic interventions
- **Cognitive behavioural therapy** (Howard C, Dupont S. The COPD breathlessness manual...in patients with chronic obstructive pulmonary disease. NPJ Prim Care Respir Med 2014; 24:14076.)

FUNCTIONING

Adaptive

- Exercise and activity encouraged
- Maintain social contact
- Self-efficacy
- Modify/maintain role


Maladaptive

- Restrict activity
- Social isolation
- Helplessness
- Receipt of help
- Reduced role

- Remember the carer. Involve them in education about, and practice with the interventions.
- Key role for clinician: where address breathlessness in addition to disease = maximise Breathing Space (Hutchinson A et al Eur Resp J 2017)

Breathlessness ladder

- First step
 - ✓ Optimise treatment of the underlying disease
- Second step
 - ✓ Non-pharmacological measures (pulmonary rehabilitation; exercise; cognitive behavioural therapy; fan; pacing/prioritising; anxiety management; relaxation; pursed lip breathing; diaphragmatic breathing)
 - ✓ Education and support for family carers
 - ✓ Crisis plan
- Third step
 - ✓ Consider low dose sustained release oral morphine (NB – remember laxatives and manage side-effects; judging increased exercise tolerance)



Or do
we??

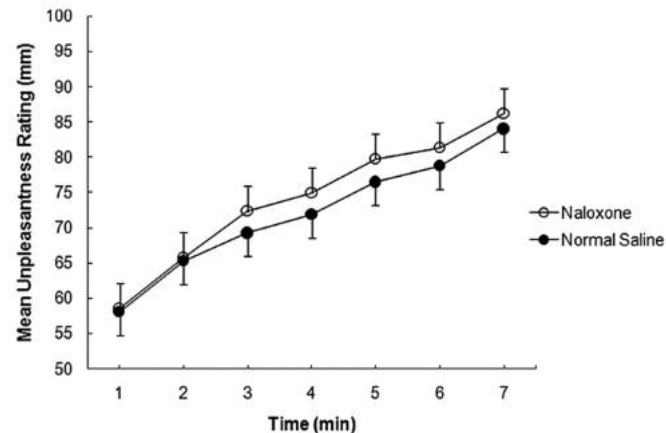
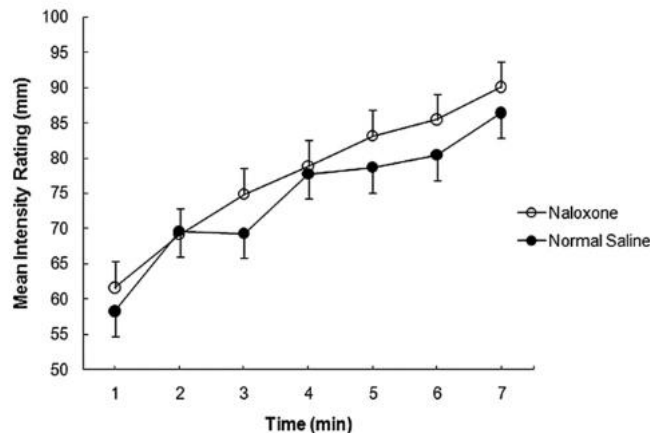
Pharmacological interventions

ERS statement – non-malignant disease 2024

- We suggest not using opioids for the treatment of breathlessness in people with serious respiratory illness (conditional recommendation against the intervention, very low certainty of evidence).
 - However, when clinicians are considering prescribing opioids ...clear communication and shared decision making between clinicians and patients are required considering:
 - benefits and harms, and active discussion and plans to manage side effects.
 - patients' goals and willingness to use an opioid medication,
 - their understanding of how to take the medication correctly, and the broader impacts on their lives (including the ability to drive) and other potential harms.
 - clinicians and the patients' informal caregivers may require education and support regarding the use of opioids

Opioids and central modulation

- Breathlessness perception is processed in brain areas rich in opioid receptors.
 - von Leupoldt A., et al. Neuroimage 2009; 48(1):200-206.
 - Reeves KC et al. Front. Mol. Neurosci 2022; 15: <https://doi.org/10.3389/fnmol.2022.919773>
- Endogenous opioids reduce breathlessness, the opioid antagonist, naloxone, increases exertion-induced breathlessness.
 - Gifford AH, et al. COPD 2011; 8(3):160-166.
 - Mahler DA, et al. Eur Respir J 2009; 33(4):771-777.

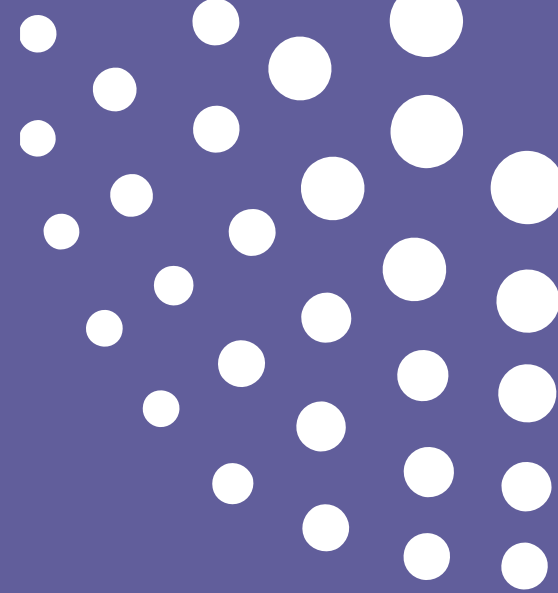


fMRI studies

- Remifentanil reduces the sensation, “urge to breath”
 - Pattinson KT, et al. J Neurosci 2009; 29(25):8177-8186.
- The brain creates expectations and beliefs (psychological “priors”) which then influence the perception of incoming breathlessness sensations; Faull OK, et al Cortex 2017; 95:211-221.
- Opioids suppress conditioned anticipatory brain responses to breathlessness; Hayen A, et al Neuroimage 2017
- In people with chronic breathlessness (using morphine) and healthy volunteers (remifentanil), worse mood reduces breathlessness response to opioids: as depression and anxiety increases, so opioid responsiveness decreases; Abdallah SJ, et al. Eur Respir J 2019; 54(3).

Summary basic science

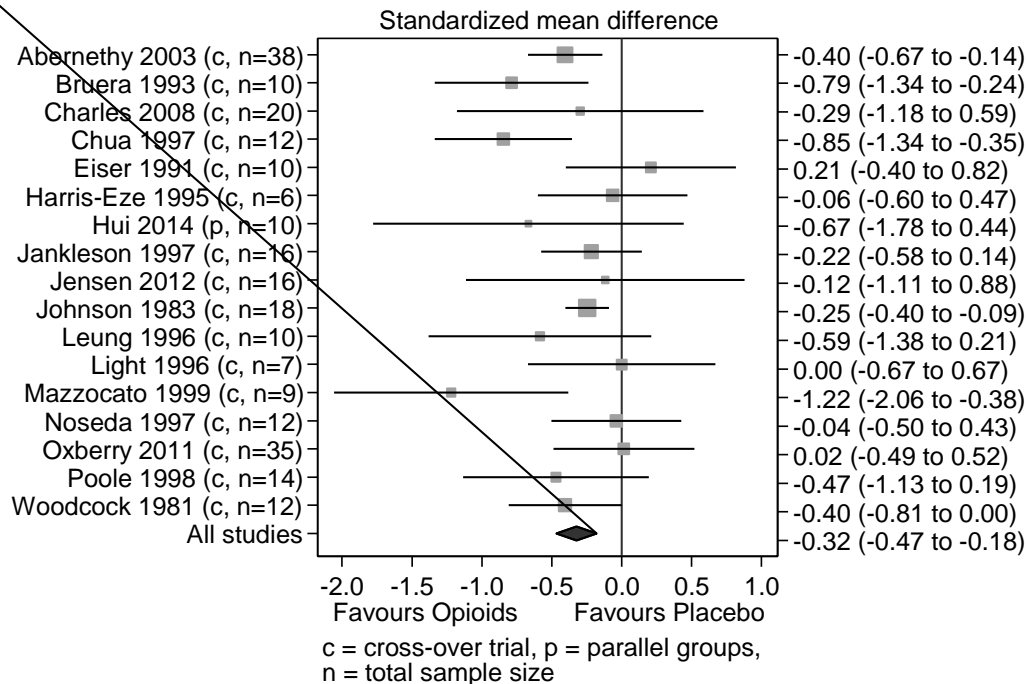
- Endogenous opioids modify perception of breathlessness
- Evidence for a central modulation is the dominant feature
- Opioids reduce the sensation “urge to breathe” through central mechanisms
- The response to opioids is reduced by impaired affect (anxiety, depression)
- Opioids appear to be able to modulate anticipatory breathlessness as well as the sensation of breathlessness itself



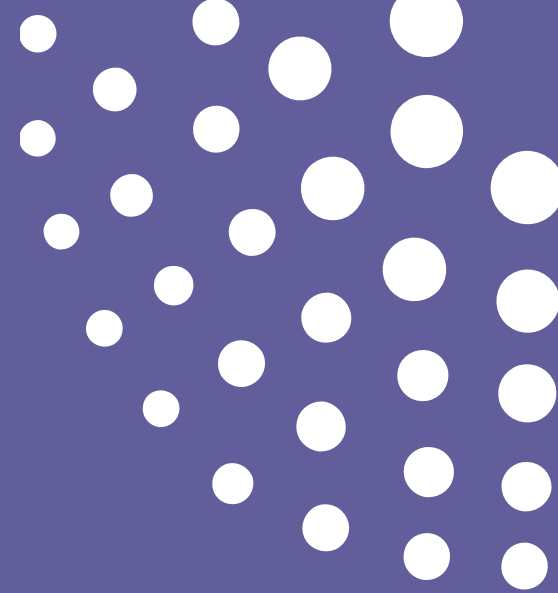
Why look at laboratory and daily life trials separately?

Systematic review and meta-analysis - all diagnoses

Ekstrom M et al. Thorax 2017

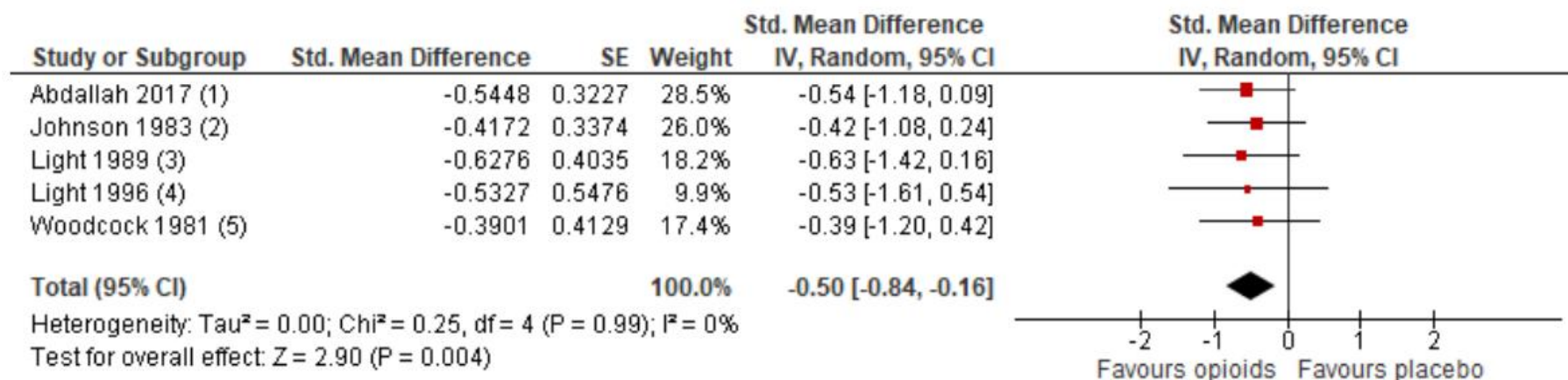


**BUT – 2017 –
new data
show opioids
don't
work...?**



Laboratory evidence of exogenous opioids

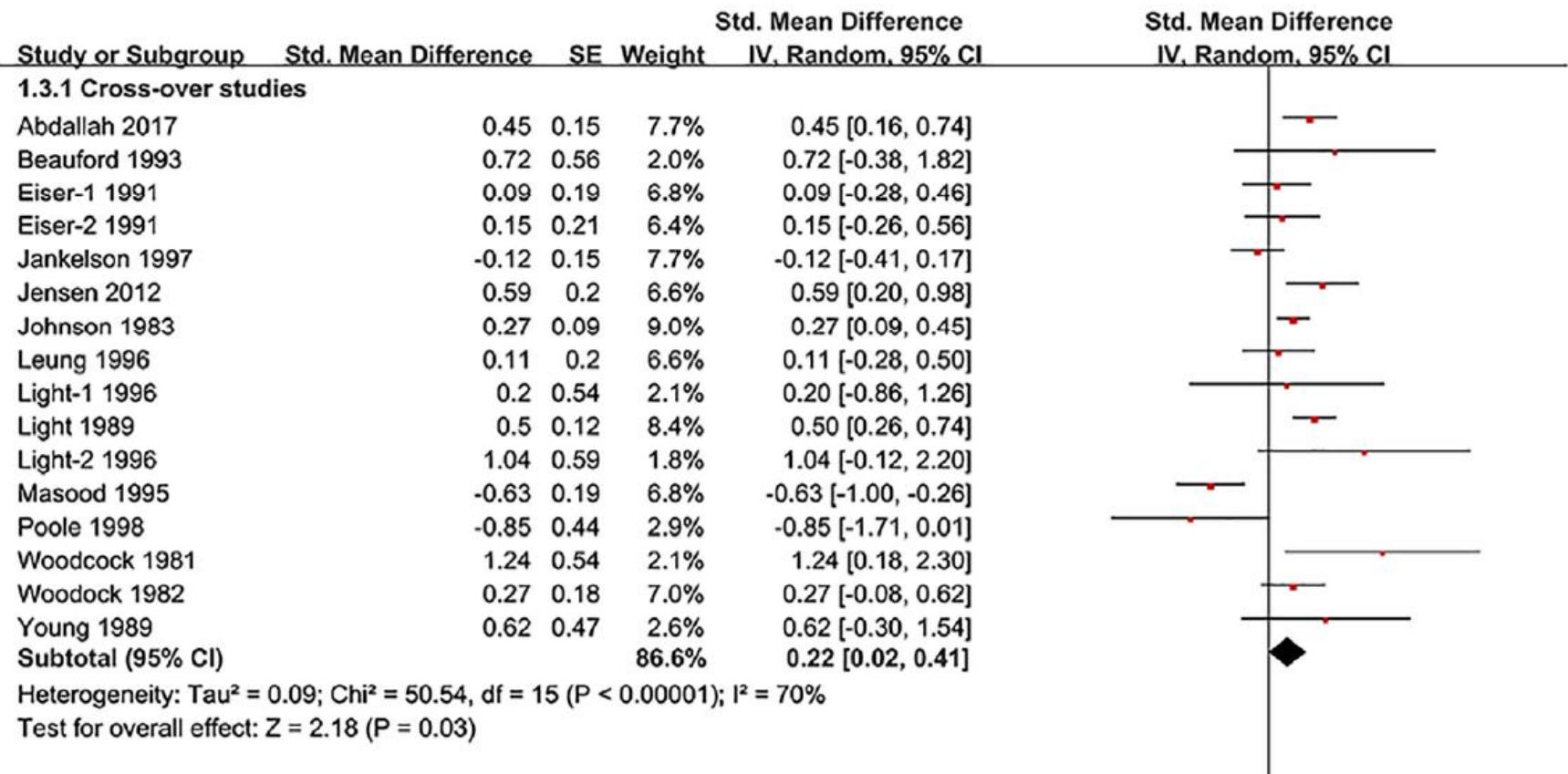
Laboratory studies measuring breathlessness at iso-time or iso-load



Holland AE, et al. European Respiratory Society Clinical Practice Guideline; ERJ 2024

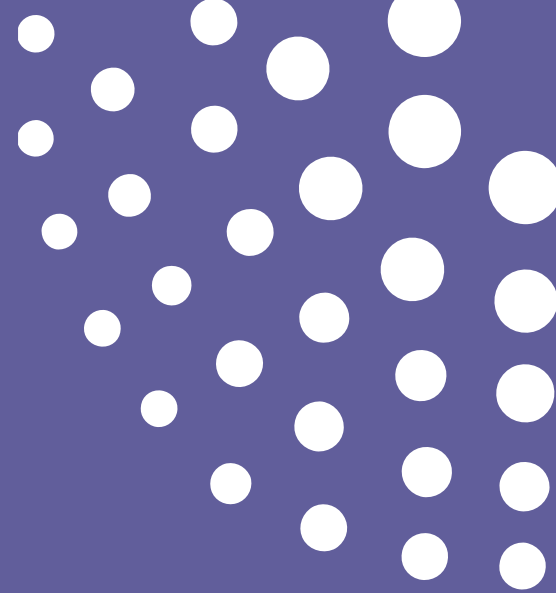
Opioids - outcome exercise endurance – improved with opioids;

Lui et al Pall Med J 2023



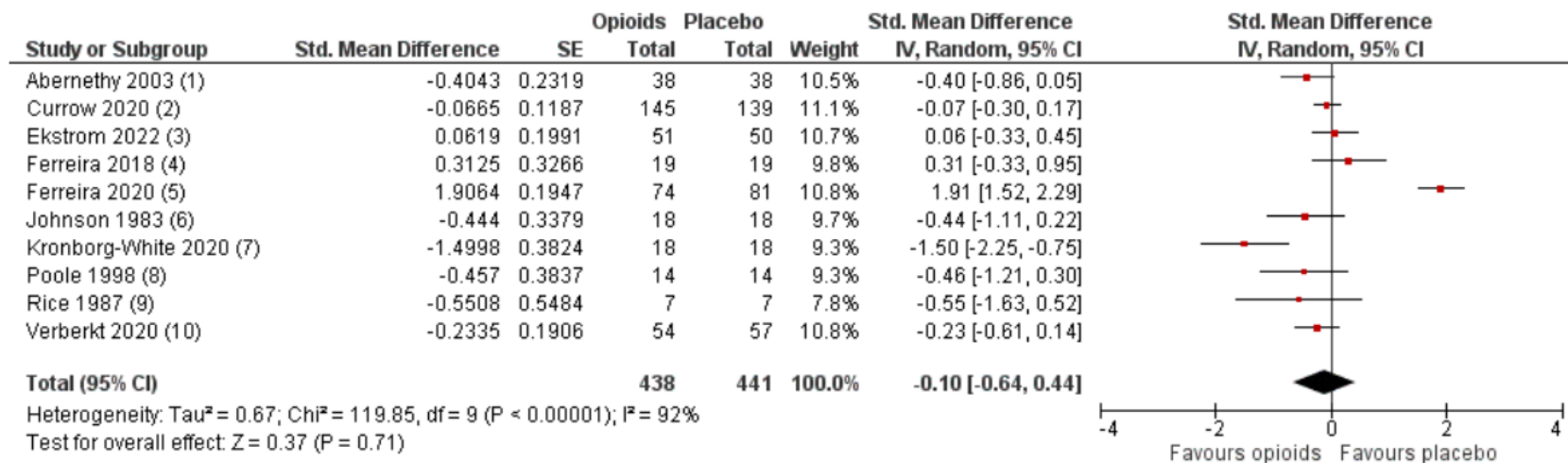
Summary laboratory studies

- opioids reduce breathlessness
- opioids increase exercise endurance
- when measured at isotime or with isoload
- **There is a strong relationship between breathlessness and physical and emotional exertion**



Daily life trials

Pragmatic studies measuring breathlessness during 'daily life'



Holland AE, et al. European Respiratory Society Clinical Practice Guideline; ERJ 2024

Messages?

- No evidence of benefit for breathlessness perception
- However, consistent signal of benefit in those with more severe breathlessness
- mixed findings with the few that had an activity component but,
 - Used non-isotime and self-regulated test such as 6MWT, or average daily steps, so exercise endurance benefit can be missed
 - Signal of benefit seen with some 6MWTs, or more detailed analysis of actigraphy (beyond the average daily steps)

Ferreira et al BEAMS substudy ERJ 2022

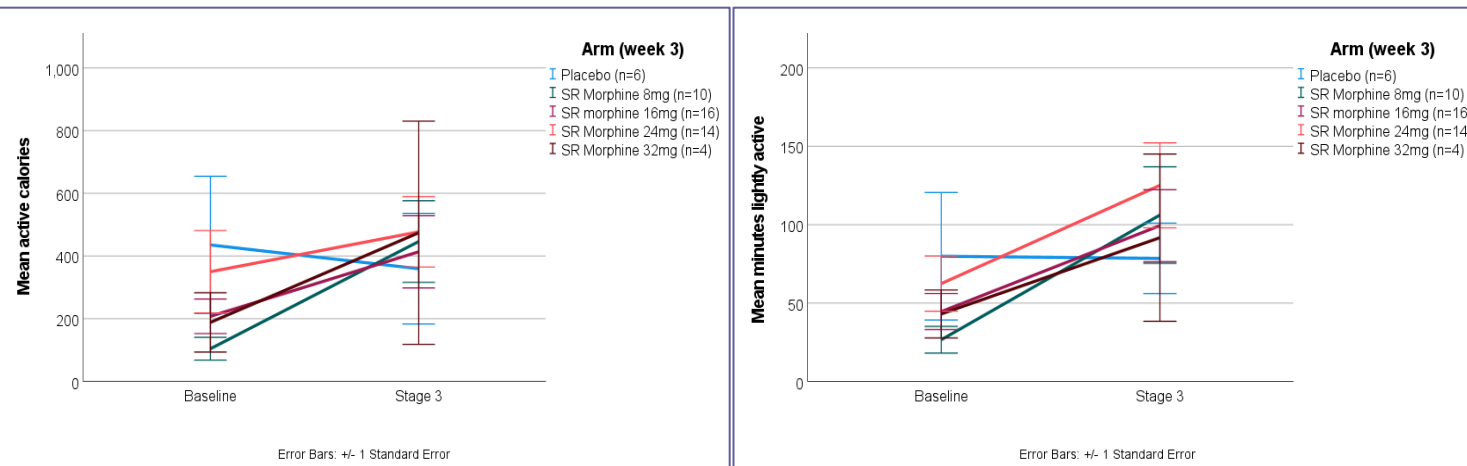
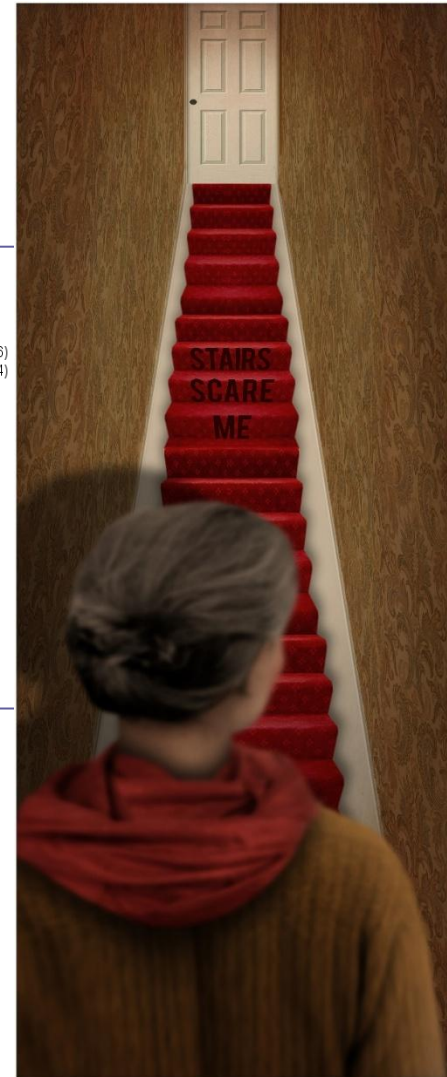


Figure 1 – Arm differences in mean activity calories (*left*) and mean minutes lightly active (*right*) from baseline to the end of week 3. (FitBIT measures)

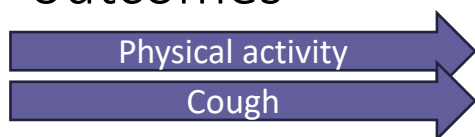
Signal of benefit in mean active calories at 3 weeks. In morphine groups



MABEL trial

Primary
outcome

Secondary
outcomes



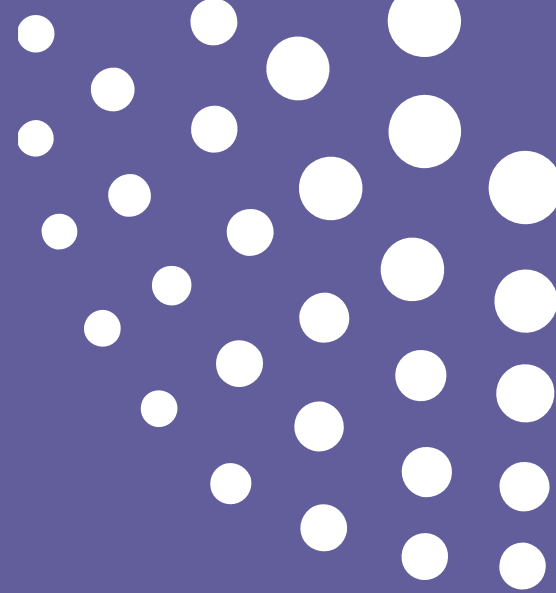
Measure	Day	Adjusted mean difference (95% confidence intervals)	p value
Worst breathlessness (NRS 0-10)	28	0.09 (-0.57, 0.75)	0.781
	56	-0.26 (-0.93, 0.42)	0.453
	Overall effect	-0.20 (-0.60, 0.20)	0.322
Levels of physical activity (minutes/day)	28		
sedentary		-21.4 (-78.1, 35.30)	0.456
light		11.96 (-17.4, 41.34)	0.421
moderate/vigorous		9.51 (0.54, 18.48)	0.038
Cough (NRS 0-10)	28	-0.36 (-1.11, 0.40)	0.353
	56	-1.41 (-2.18, -0.64)	<0.001
	Overall effect	-0.70 (-1.22, -0.17)	0.009

Probability of cost-effectiveness at £20,000 NICE thresholds = 65% at Day 28

Scenario based analysis excluding non-related SAEs = 88% at Day 28

MABEL trial - so what?

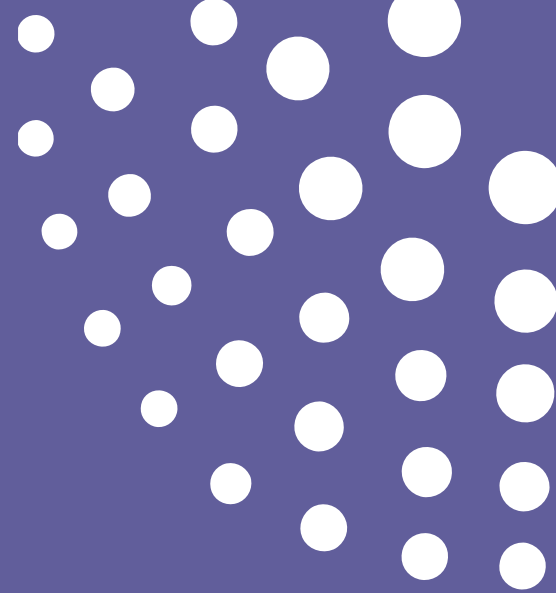
- Consistent with other 'daily life' trials without an isotime/load measure of breathlessness
- Further supports evidence of better exercise endurance
- Further supports evidence of benefit for cough
- Small QoL improvements, but enough to give a favourable health economic evaluation (assuming attribution is correct)
- Dose regimen (start at 5mg MST BD) with close monitoring and early management of expected side-effects gives better tolerability



Safety

Safety

- Trials to date – side-effects mild, expected and self-limiting mainly during the 1st week – but ongoing monitoring is necessary, ...
- Morphine has a known safety profile and should be prescribed i) for the right patient, ii) with due care in monitoring; same for beta blockers, ACE-inhibitors, beta agonists, anti-diabetic medication, digoxin, ...
- Beware constipation – breathlessness could get worse...
- Don't assume non-palliative care clinicians know how to initiate or monitor opioids
- Common sense care re driving (awaiting BEAMS subgroup study findings)
- Beware fluctuating renal function (morphine)



SUMMARY

VERDICT

- Do opioids improve breathlessness and exercise endurance in laboratory trials? **YES**
- Do opioids improve breathlessness at rest in clinical study? **YES (Abernethy et al)**
- Do opioids improve exercise endurance in ambulant people with moderate to severe breathlessness? **MAYBE**
- How to capture benefit in those who are ambulant and comfortable at rest?
 - Once physical exertion starts to complicate the situation, a primary measure of breathlessness may be less helpful
 - Unless breathless at rest, need a standardized exercise endurance test
- **THE MORPHINE STORY IS NOT FINISHED YET....**

Thank you

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<https://www.hyms.ac.uk/research/research-centres-and-groups/wolfson/breathlessness/bringing-breathlessness-into-view-exhibition>

