SEDA

Supportive care, Early Diagnosis and Advanced disease research group

Lifting the veil on breathlessness

Scottish Partnership for Palliative Care

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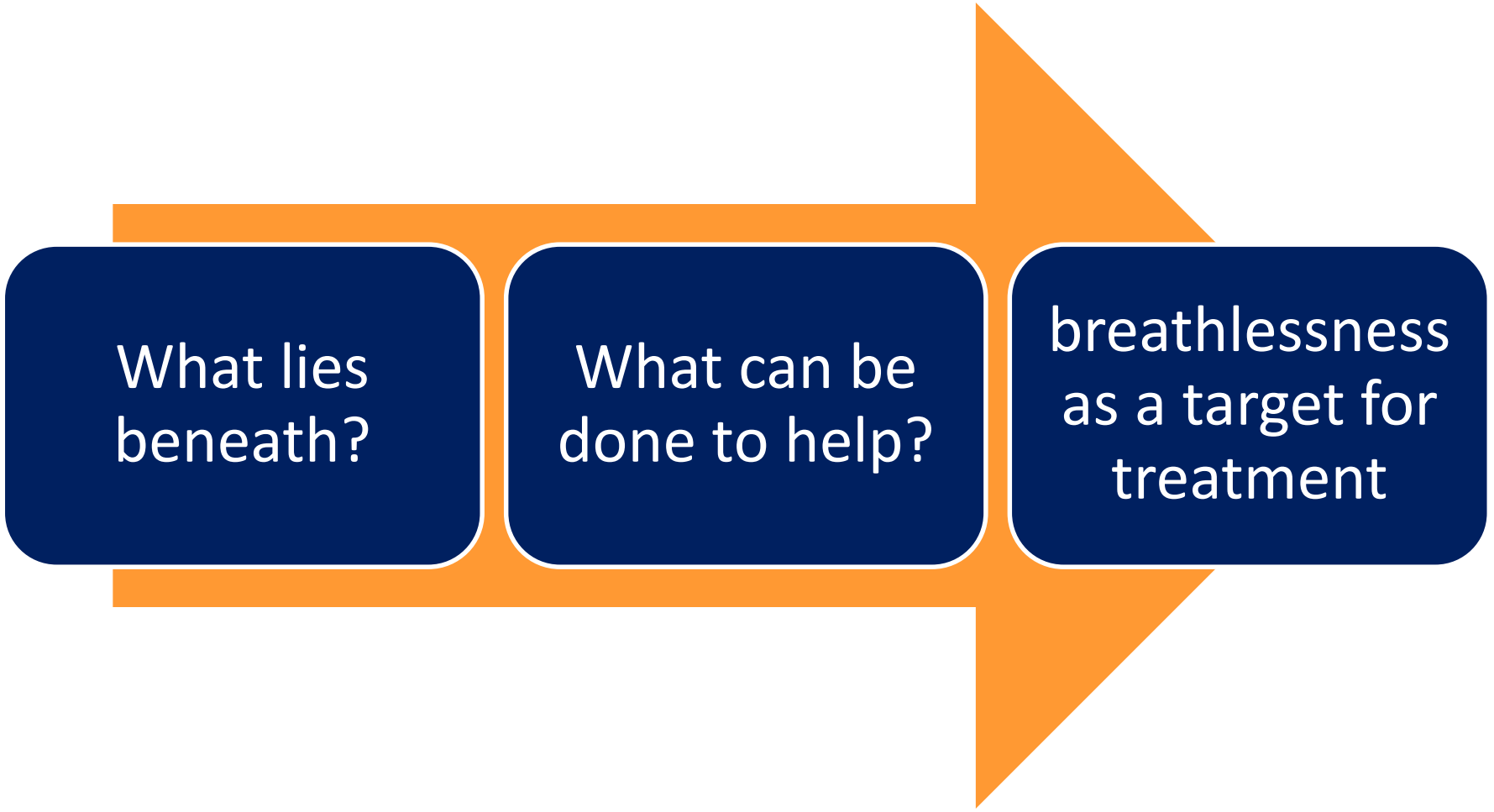
THE HULL YORK MEDICAL SCHOOL

definitions

- (ATS) consensus statement: “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity, that derives from interactions among multiple physiological, psychological, social and environmental factors, and may induce secondary physiological and behavioural responses”

Overview


What lies beneath?
What can be done to help?
breathlessness as a target for treatment

How common is breathlessness?

- 9 to 61% (definition and population studied)
  - General:
    - Australia 9% *chronic* breathlessness
    - England 15% of men and 26% of women
      - "On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace"
    - Norway 13%
      - at least "moderate dyspnoea on exertion"
- More commonly reported by older people
- More commonly reported by women

Breathlessness due to chronic heart and lung conditions

- Cancer: 10 to 99%
  - Can be breathless without lung involvement
- Heart-lung diseases
  - 60 – 88% (heart failure)
  - 90-95% (chronic obstructive pulmonary disease)
- Gets worse as the illness gets worse

Do patients tell us?

- interviews with 18 people with COPD;
  - all reported delaying medical help until there was a crisis
  - crisis led to a diagnosis and treatment of COPD,
  - but the *refractory* breathlessness was managed by themselves rather than by seeking further medical help

Gysels et al JPSM 2010

Ways round the problem… but at a cost

"Well it just becomes part of my life, it is my life, unfortunately, but it is my life…" (Johnson M FAB study)

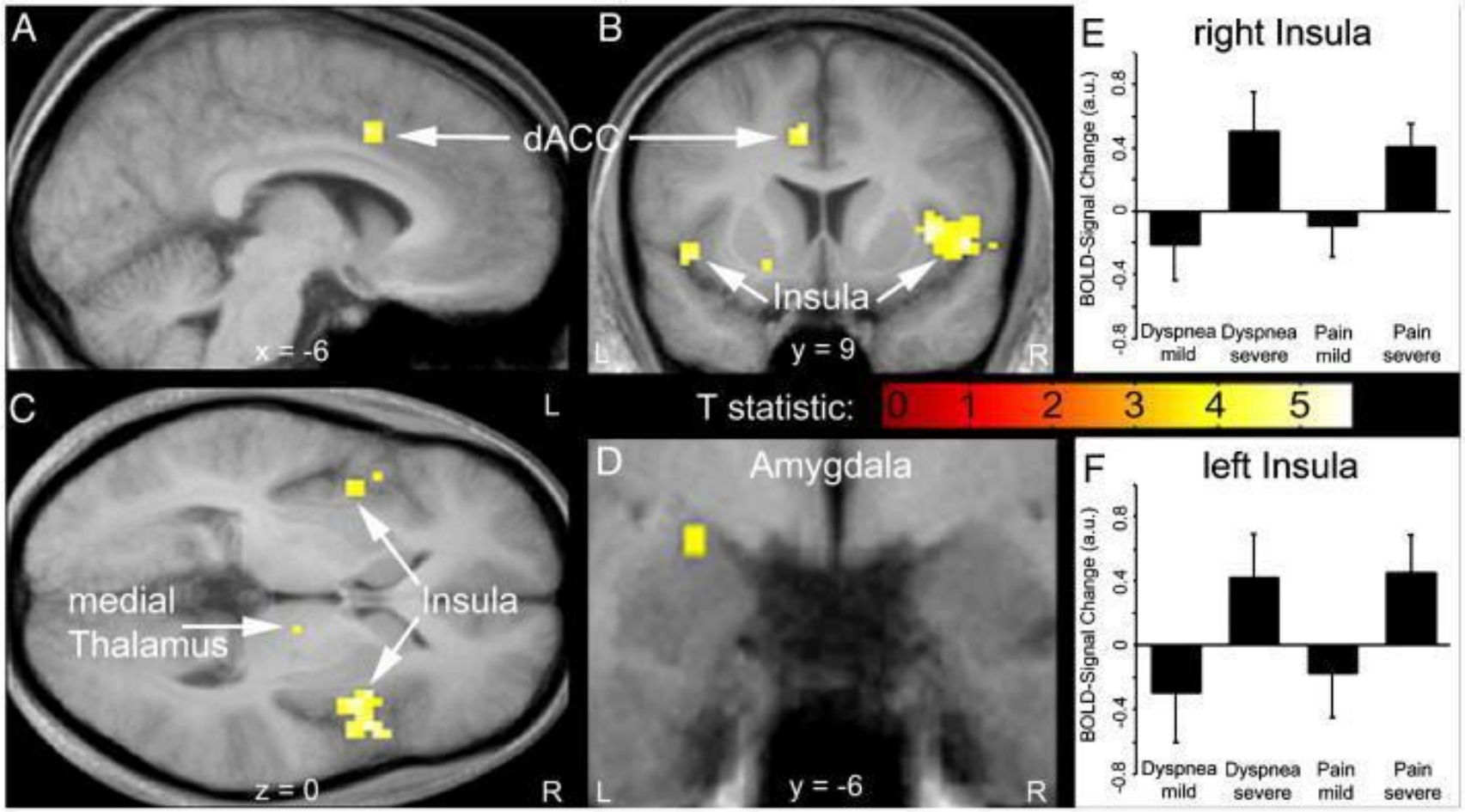
"… I've always been used to doing the manly things, like carrying out the rubbish, …now I have to watch her take that out. I have to watch her cut the grass, I have to watch her doing the heavy lifting and, you know, that, that drives me potty ..." Oxberry S et al Postgrad Med J 2011


What can be done to help?

Understand what is going on…

- How does our brain “know” if we are breathlessness
- Understand mechanisms and find targets for treatments

What's going on in the brain?

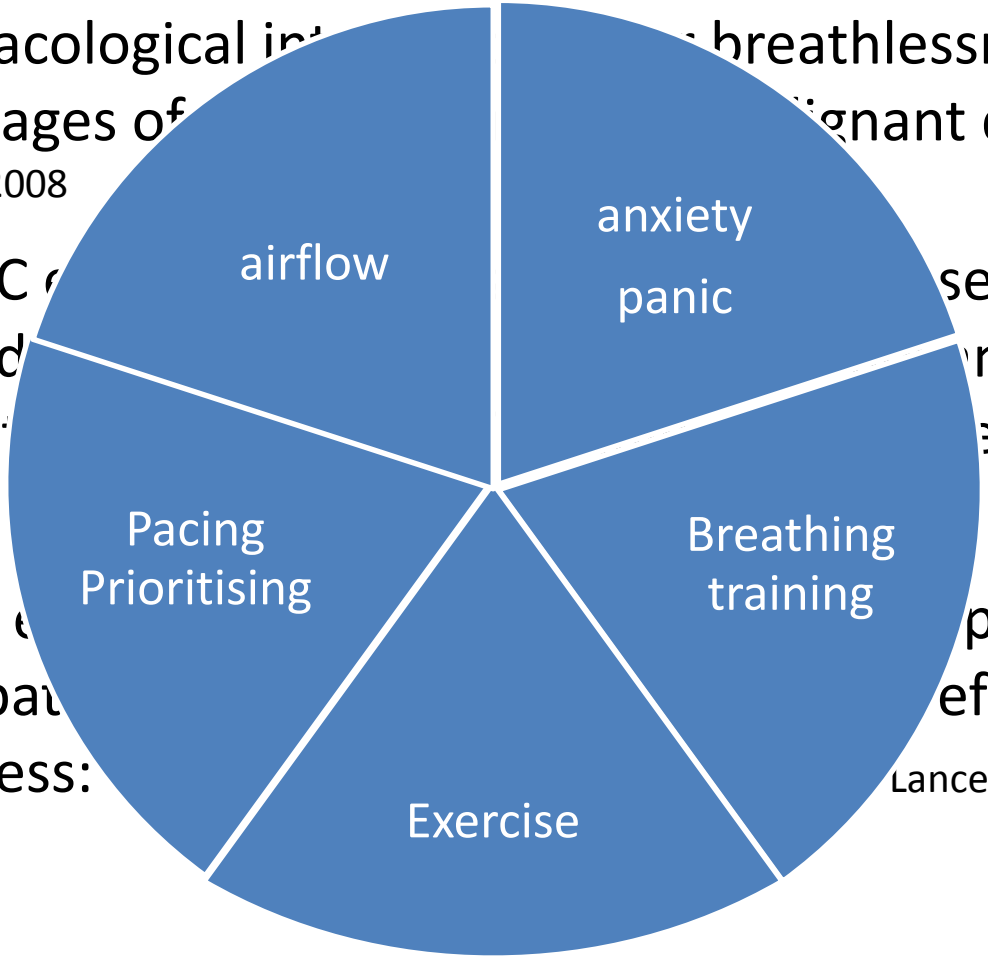


von Leupoldt et al. NeuroImage 2009; 48:200–206

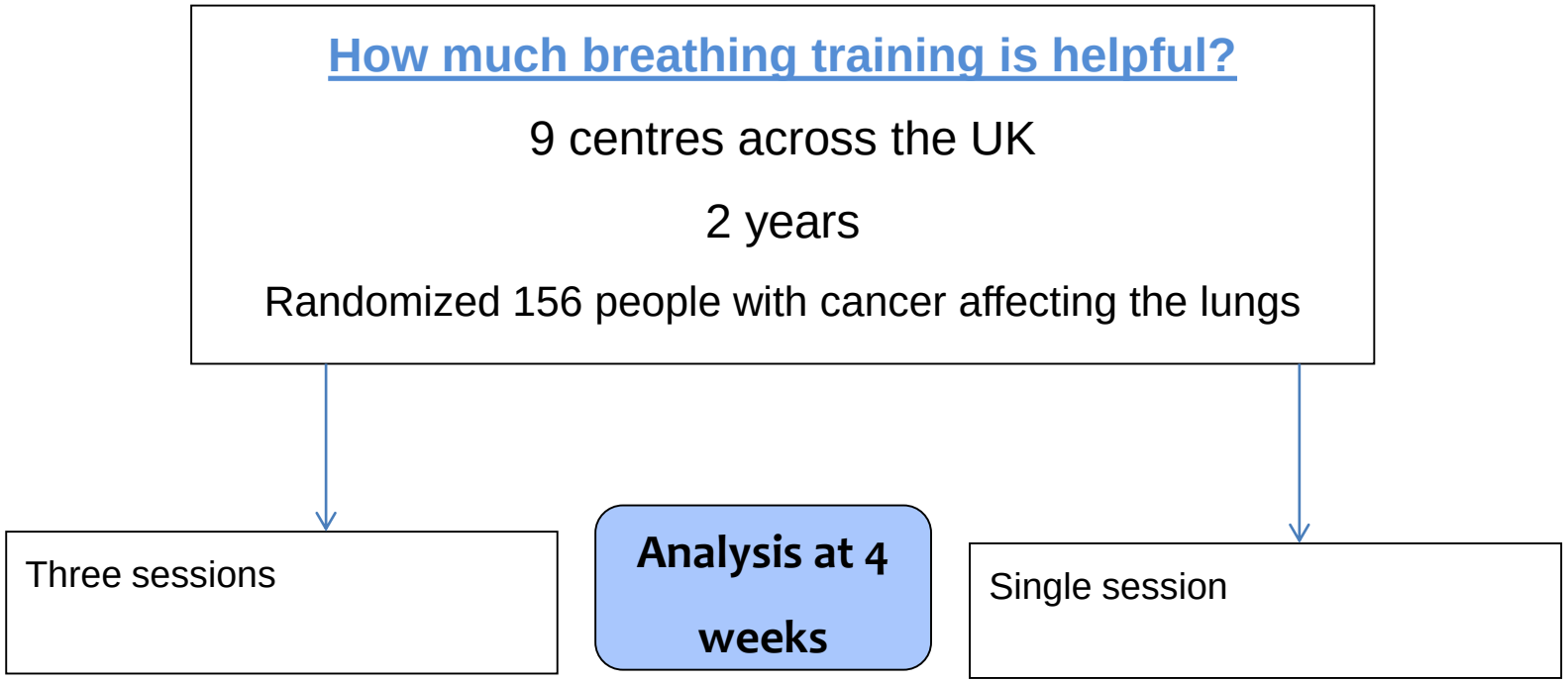
Acute versus chronic breathlessness – Johnson M et al Magnetoencephalographic scanning BMJ Open 2015

Evidence based – complex interventions for refractory breathlessness

- Non-pharmacological in… breathlessness in advanced stages of …ignant diseases Bausewein C et al Cochrane 2008
- Farquhar MC … service more effective and … nced cancer and their carers … ed-method randomised …
- Higginson IJ … piratory care service for pat… efractory breathlessness: … Lancet Respir Med 14 A.D.



Shortness of Breath Trial



Johnson MJ et al BMC Medicine 2015

Funding from the NIHR Research for Patient Benefit

results

Primary outcome:

- Overall , the “worst” breathlessness/24 hours score reduced from 6.8/10 at baseline to 5.8/10 at week 4.

- no difference between the two groups (area under curve):
  - three sessions 22.86 *vs* single session 22.58; P = 0.83;

No difference in any secondary outcomes except:

- AUC for “distress” = three 16.2 *vs* single 12.3; P = 0.01 even when controlled for baseline values.

Conclusions and impact

- Three treatment sessions conferred no additional benefits over a single session and was not cost-effective.
- Reducing the burden of healthcare appointments is an important part of care.
- Our local service now routinely offers a single session to people with lung cancer

Opioids - Do they help?

- 1 Cochrane review of the literature:
  - Jennings AL et al Thorax 2001(all causes of breathlessness)

All support the use of morphine and diamorphine for the relief of breathlessness by the oral or parenteral route.

Since the Cochrane review..

- 1 phase 3 placebo RCT(multiple causes)
  - Morning VAS* 6.6mm; evening VAS 9.5mm improvement
    - Abernethy AP et al BMJ 2003
- 1 pilot placebo RCT(heart failure)
  - VAS improved with morphine by 23mm by D2 vs 13mm with placebo
    - Johnson MJ et al EJHF 2002
- 1 phase 3 placebo RCT (morphine/oxycodone, heart failure)
  - All arms improved, none better than the others
    - Oxberry SG et al EJHF 2011

*VAS = visual analogue scale 0 – 100mm line (no breathlessness = 0; worst possible = 100)

Does a 9mm change matter?

- 3 placebo controlled studies of morphine for breathlessness
  - Blinded patient preference at end
  - Asked to choose the arm; breathlessness best
  - A additional improvement of 9mm was enough for a patient to choose one intervention over another

Johnson MJ, Bland JM, Oxberry S, Abernethy A, Currow DC. Clinically important differences in chronic refractory breathlessness. JPSM 2013, 46: 957-963

3 month open label follow up of patients completing RCT (Oxberry et al JPM 2012)

- Improvement in NRS breathlessness and global impression of change in those who took open label opioids compared with those who did not

BreatheMOR-HF

Morphine for breathlessness in heart failure

- 346 people with heart failure and refractory breathlessness
- Randomly allocated 20mg modified release morphine per day or placebo
- 1 month efficacy; 3 months toxicity
- Measures: breathlessness intensity, activity
- Funding British Heart Foundation

Phase II Dose titration and Phase IV pharmacovigilance

- 1 dose finding study
  - 10 – 30mg MR morphine titrated for one week then long term on the dose of clinical benefit
  - Approximately two thirds net benefit
- Of those who improved, over 90% did so by 20mg per day

Currow DC et al JPSM 2011

Opioid therapy in COPD

Ekström et al. *Ann Am Thoracic Soc 2015*

- Review and meta-analysis 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
- Meta-analysis
- Breathlessness was reduced : standardised mean difference (SMD)
  - steady state -0.44 (95% CI, -0.68 to -0.19)
  - all studies - 0.30 (95% CI, -0.59 to -0.02)

Safety of low dose oral morphine

- Safety of Benzodiazepines and Opioids in Very Severe Respiratory Disease: A National Prospective Study. (Ekström M et al BMJ 2014)
  - N= 2249 LTOT; followed for 4 years
  - With ≤30mg oral MEDD
    - No increased risk of mortality (HR 1.03 [95% CIs 0.84 – 1.26])
    - No increased risk of hospitalisation (HR 0.98 [0.86 – 1.10])

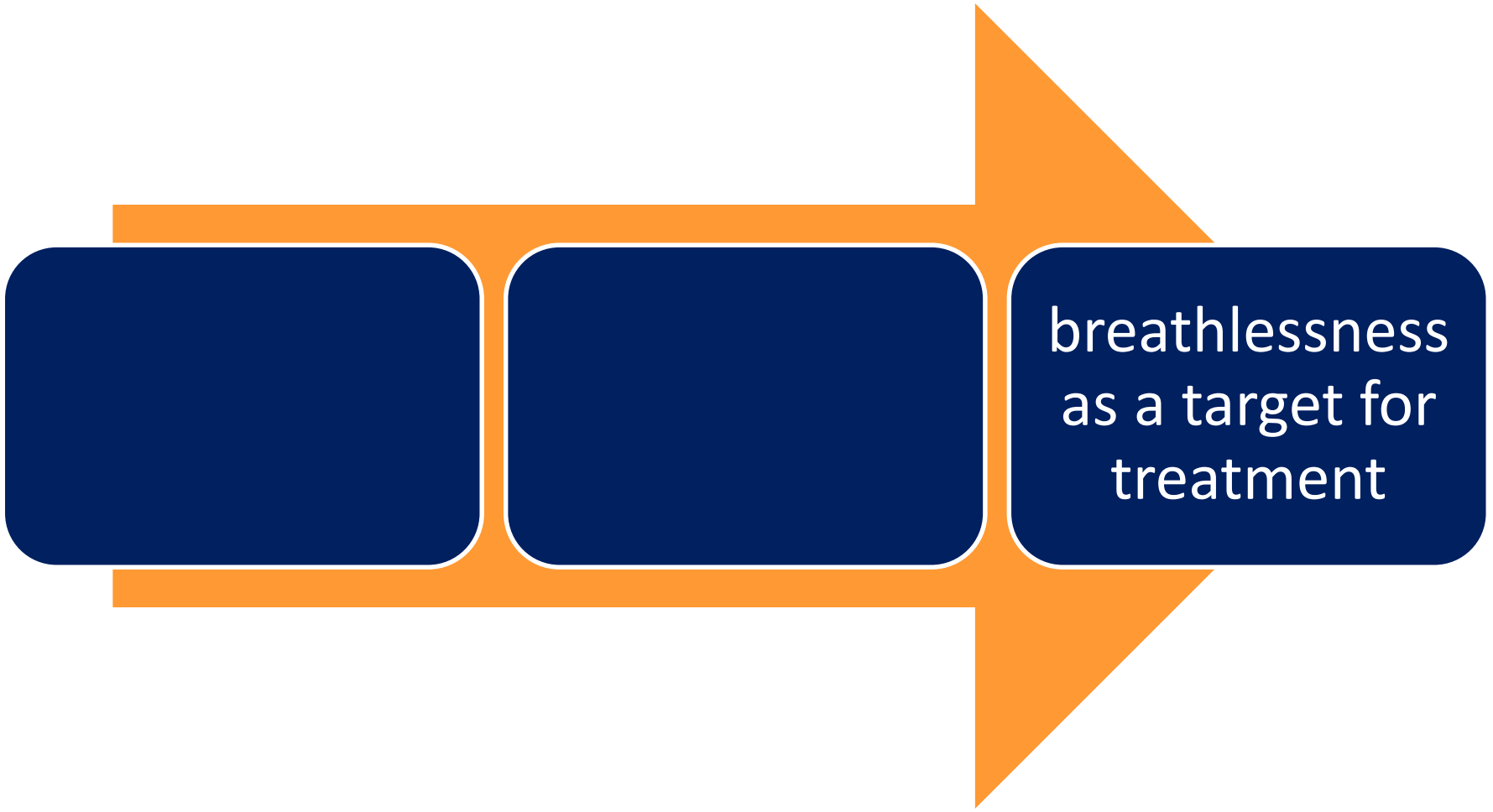
Breathlessness – opioid titration in people already on opioids

- Pairs given in random order 25% or 50% of 4 hourly IR dose of morphine
- Follow up for 4 hours

- In people with cancer already on opioids for pain with persistent dyspnea, 25% of the equivalent 4-hourly dose of opioid may be sufficient to reduce dyspnea intensity for up to four hours

Allard P et al. J Pain Symptom Manage 1999 Apr;17(4):256-65.

The way forward



Condition or symptom?

- **If neither patient nor clinician sees refractory breathlessness as a target for treatment:**
  - **Poor access to proven interventions for refractory breathlessness**

Bringing breathlessness above the surface

- Need to bridge the credibility gap for patients and clinicians…
  - Identify the true size of the iceberg
  - Mechanisms
  - Continue to build the evidence base
  - Measure routinely in clinical practice
  - Put treatments into practice
- Aim: effective therapies for breathlessness alongside therapies directed at the condition

Johnson MJ, Currow DC, Booth S, Prevalence and assessment of breathlessness in the clinical setting. Expert Review of Respiratory Medicine 2014 1-11

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To leave the world a bit better; to know that one life has breathed easier because of you. This is to have succeeded

~ Ralph Waldo Emerson

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