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Breathlessness: what we know, and what we don't know

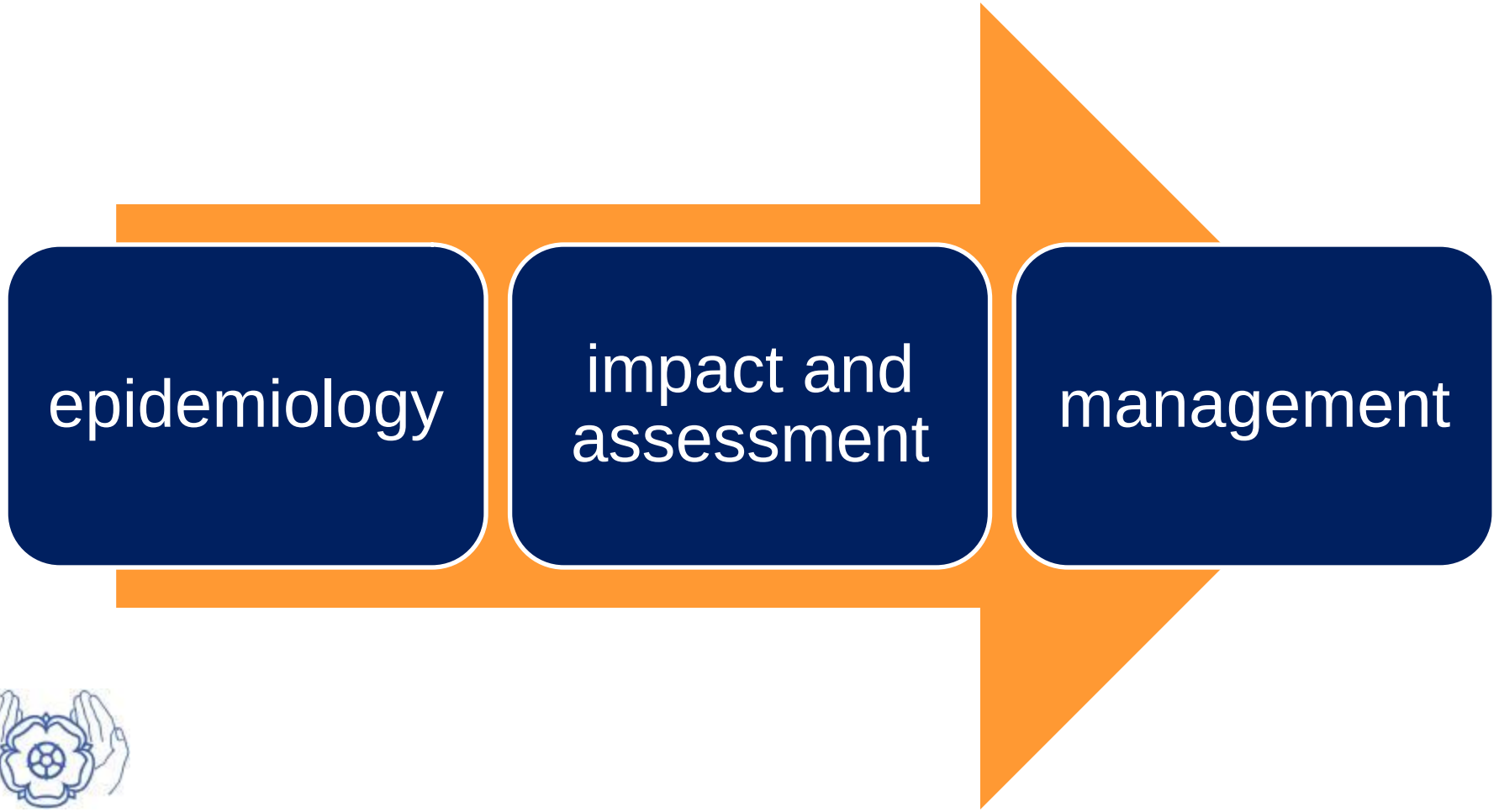
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ST CATHERINE'S HOSPICE

Overview

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ST CATHERINE'S HOSPICE

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”

Refractory

- Breathlessness persists despite optimal treatment for their underlying condition, and after any potentially reversible complications have been addressed.

- 123 patients presenting to primary care with chronic breathlessness (>8 weeks) (Pratter 2011)
  - a diagnostic algorithm
  - diagnosis 99%,
  - breathlessness improved in 63% with treatment of the primary condition
  - 37% remained with refractory breathlessness

Epidemiology - population

- 9 to 58% (definition and population studied)
  - General:
    - Australia 9% *chronic* breathlessness (mMRC dyspnea scale ≥ 1)
    - England 2011 (≥ 2 MRC dyspnea scale);15% of men and 26% of women
    - Norway 13% with “moderate dyspnea on exertion” and 5% with “severe dyspnea on exertion”
  - Older age:
    - Koreans 60 – 69: men -38%/28% smokers/non-smokers;
    - Ireland >70: MRC Dyspnea scale ≥ 3; 32.3%
    - Denmark 60 -79 : 37%
  - Persistent gender divide: F>M

Epidemiology - chronic cardio-respiratory conditions

- Worsens in advanced disease/ the weeks prior to death
- Cancer: 10 to 79% depending on the tumour site, stage and setting.
  - Can be breathless without pulmonary involvement
- Estimates for non-malignant cardio-respiratory diseases range from
  - 60 – 88% (heart failure)
  - 90-95% (chronic obstructive pulmonary disease)

Primary care – reasons to go to the doctor

- Dutch cohort: 1% (Frese T et al J Clin Med Res 2011)
- Australia: 1% (Currow D et al PLOS ONE 2013)
  - breathlessness more common in women
  - >1/3rd ; >75 years
  - >3x home/care home consultation; 2.5 x more likely to be referred urgently to the ED

Emergency departments

- US: 2.7% of all presentations, (National Hospital Ambulatory Medical Care Survey: 2010 Emergency Department Summary Tables)
  - >65, 2nd most common reason (4.0% women and 3.1% men). 1st = Chest pain (4.5% women and 3.3% men).
- Norway: 9% (Langlo, N. M et al Eur J Emerg Med (2013))
  - 3rd most common cause after abdominal pain (13%) and chest pain (13%)
- Irish palliative care patients: 25% (Wallace EM 2013 Am J Hosp Palliat Care)

Do patients tell us?

- Population studies: patient report
- All other studies: clinical record
- Qualitative work: (Gysels M JPSM 2010)
- interviews of 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

Epidemiology -what don't we know?

- Patient *self-assessed* prevalence of breathlessness in primary care, ED, acute admissions unit, general wards
- How common?
  - Under-reporting by patient; if so, why?
  - Poor recognition by clinician
- What is the presentation pathway?
- If neither patient nor clinician sees refractory breathlessness as a target for treatment, then is it assumed nothing more can be done?
  - Access to evidence based interventions for refractory breathlessness?

What can you go to the doctor for?

Gysels M et al JPSM 2010

"So it's gradually, little things were in my head but not enough to go to the doctor. You can't go to the doctor and say ''I can't dance.'' It's a strange thing to say to the doctor."

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Clinical impact – key outcomes

- **Survival:**
  - US population study; mortality ratio of 2.08 at 2.5 years
  - Norwegian cohort 30 year follow up; association with all cause mortality
  - Advanced cancer with breathlessness presenting to the ED; worse 90 and 180 day mortality
  - Community based cohort >70; poorer 2 year and 10 year survival
- **Admission**
  - Breathlessness presentation at the ED; 88% of people with heart failure, 60% with COPD admitted to a hospital bed
  - Routine NRS 0-10 measurement of breathlessness on arrival to ED; predictor of admission (≥ 8/10) or discharge (≤ 3/10)
- **In-hospital adverse event**
  - Breathlessness in acute medical patients > 4 NRS: predicts in-hospital serious events

Restrictions…

Oxberry S et al Postgrad Med J 2011

"… 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 ..."

Clinical impact

- Retreat into own homes
- Reduce exercise
- Social isolation
- Invisible – but don’t want to be visible
- Poor access to services
- Adapt/manage using own resources

Assessment of dyspnea: understanding and measuring

- Important understanding of patient and carer experience from other qualitative data
  - Invisible
  - Poor access to services (Gysels M et al)
- Important understanding of the challenging nature of breathlessness
  - Episodic breathlessness (Simon S et al: SLR, interviews, Delphi)

Assessment

- focus on breathlessness as a clinical sign
  - Visible, with laboured respiration and raised respiratory rate
- investigation algorithm
- focus on diagnosis directed treatment
- assessment of the breathlessness itself is rarely done in regular practice
- unlikely to have a full assessment of refractory breathlessness

Assessment – refractory breathlessness

- Need for individually tailored assessment
- Some consensus
  - unidimensional/multi-dimensional (Bausewein 2006; Dorman 2008)
- Perception (intensity/unpleasantness) *and* emotional response
- Relate to function
- Baseline and review important to assess effect of interventions
- Linked to education and action – *routinely embedded in clinical practice*

What improvement is improvement?

Johnson MJ et al. 2013 JPSM

- Assessed clinically important difference using two methods
- Distribution method
  - Effect size: change in mean score from baseline/SD baseline scores
  - different study populations should have a similar level of precision over the perception of study measure and in a change in that measure
- Patient anchor
  - Choice of one intervention over another

[Guyatt GH et al Methods to explain the clinical significance of health status measures. Mayo Clin Proc 2002 Apr;77(4):371-83.]

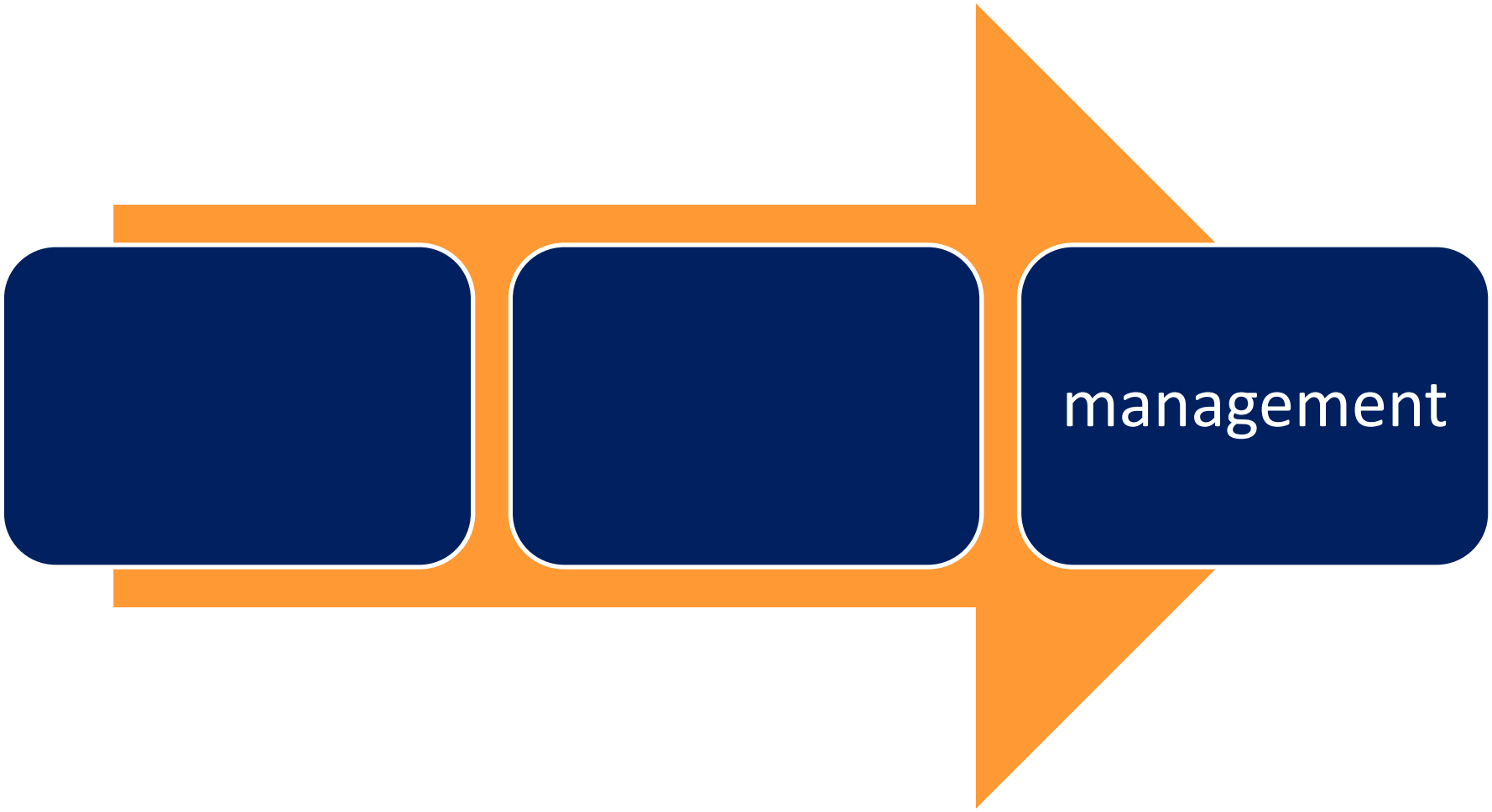
Detectable/important?

- Groups can distinguish the change, but what does it mean?

- Patient anchor: blinded preference
  - participant preference change in VAS was **–9mm** (95% CI −15.8 to −2.1) (p = 0.008).

  - That is: a 9mm greater benefit was enough to result in patient preference for one intervention over another

Overview



Skeletal muscle and dyspnoea

- Muscle abnormalities in COPD and HF
  - Decreased mechanical efficiency
  - Oxidative type I shift to glycolytic type II fibres
- Lead to
  - Enhanced lactic acid production during exercise
  - Rapid decline and impaired recovery of phospho-creatine stores
- Oxidative capacity partly reversible in COPD with pulmonary rehab
- Some evidence to suggest need nutritional approach as well as exercise– eg Poly unsaturated fatty acids (PUFA)/creatine

Skeletal muscle

- Directly related to exercise tolerance, fatigue and breathlessness
- Muscle bulk is important
- Unifying picture of a link between muscles, increased sympathetic drive, breathlessness and inflammation has been put forward in HF
- Intervention to preserve muscle function or even reverse myopathy may be helpful
- A reason why people with HF may be breathlessness without pulmonary congestion

Non-pharmacological management

- Relaxation and anxiety management
- Pacing and prioritising
- Breathing training
- Goal formation
- Exercise (active or passive)

- Helps with intensity of breathlessness and the "sense of mastery"
- Non-pharmacological interventions, Systematic review
  Bausewein 2008 : 47 RCTs

airflow

- Healthy volunteers; facial airflow reduces sensation of breathlessness Schwartzstein 1987
- COPD, Airflow or nasal mucosae stimulation Liss and Grant 1988
- COPD, exercise in cool air *vs* room air: increased exercise performance and reduced end exercise breathlessness intensity Spence 1993
- COPD, treadmill + fan to face; reduced exercise induced breathlessness Baltzan 2000
- COPD, leg ergometry + fan to face: increased exercise tolerance vs fan to leg (breathlessness intensity no difference) Marchetti 2004

“placebo” arm of oxygen studies – patients who do not qualify for LTOT

Systematic reviews

- Cranston et al Cochrane Database Syst Rev 2008 (cancer, CHF, kyphoscoliosis)
- Uronis HE et al Br J Cancer 2008 (cancer)
- Uronis HE et al Cochrane Database of Systematic Reviews 2011 (COPD)
- Ben-Aharon et al J Clin Oncol 2008 (cancer)
- Booth S et al Respir Med 2004 (cancer, COPD, HF)

Powered parallel RCT

- Abernethy et al Lancet 2010 (COPD, cancer, CVD)

CHF

- Few patients in the studies have heart failure
- Evidence of benefit in sleep disordered breathing with NOT/CPAP
- OXYGEN-HF: recruiting (home oxygen, medical air, control)
  - Hospital admissions at 6 months
- HOT: recruiting (LTOT, control)
  - QoL (MLwHF)

Opioids - Do they help?

- 1 Cochrane review:
  - Jennings AL et al Thorax 2001(all aetiologies)

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

Since the Jennings review

- 1 adequately powered placebo RCT
  - Abernethy AP et al BMJ 2003 (multiple aetiology: 20mg MR morphine)
  - Morning VAS 6.6mm; evening VAS 9.5mm improvement
- 1 pilot placebo RCT(CHF)
  - Johnson MJ et al EJHF 2002 (CHF 2.5-5mg IR morphine qds)
  - VAS improved with morphine by 23mm by D2 vs 13mm with placebo
- 1 adequately powered placebo RCT (morphine/oxycodone) CHF
  - Oxberry SG et al EJHF 2011
  - All arms improved, none better than the others

Phase II Dose titration and Phase IV pharmacovigilance

- 1 dose finding study (Currow D et al JPSM 2011)
  - 10 – 30mg MR morphine titrated for one week then long term on the dose of clinical benefit
  - 83 patients (titration), 52 (pharmacovigilance)
  - Drowsiness and constipation were main adverse events
  - No cases of respiratory depression or opioid-related hospital admission
  - Approximately two thirds net benefit
- Of those who improved, over 90% did so by 20mg per day
- Mean duration in study 142 days (SD 190; median 29; range 2-665)

Benefit for whom?

- 213 individual pooled datasets
- higher baseline breathlessness intensity scores strongly predicted absolute and relative response ($p < 0.001$).
- younger age also predicted relative response ($p = 0.025$)
- functional status and dominant cause of breathlessness did not.

Johnson MJ, Bland JM, Oxberry SG, Abernethy AP, Currow DC. Opioids for chronic refractory breathlessness: patient predictors of beneficial response. Eur Resp J Published online before print December 20, 2012, doi: 10.1183/09031936.00139812

viewpoints

- Clinician survey (Rocker et al Chest 2008)
  - Doctors' fear of respiratory depression
  - Cautious unless imminently dying
  - Contact with palliative physicians increases confidence
- Patient interviews (Oxberry et al BMJ S&PC 2010)
  - Less opioiphobia than cancer patients – previous positive experiences
  - Perceived that the doctor was worried about it though
  - Faith in clinical team

benzodiazepines

- There is no evidence for a beneficial effect of benzodiazepines for the relief of breathlessness in patients with advanced cancer and COPD (Simon ST et al. 2010 Cochrane Database Sys Rev)

In summary

- Chronic refractory breathlessness is a common problem in advanced cardio-respiratory conditions
- Associated with poor clinical outcomes
- It is a hidden symptom which requires systematic assessment
- Small improvements are clinically important
- Benefit with opioids and non-pharmacological interventions.
- Little current evidence to support use of any other pharmacological intervention
- Most studies in COPD and cancer – ongoing work in HF