Breathlessness: the pain of non-malignant disease

- Breathlessness is the most common symptom of advanced non-malignant disease
- Palliative care services still less likely to work with medical teams or have confidence to manage non-malignant disease
- Breathlessness may be the symptom that offers a way in.

Science supports the Art of Medicine
Booth Palliative Medicine 27(6) 483–485

Contents

- Why is this important?
- Interventions for breathlessness
  - Non-pharmacological
  - Pharmacological
  - With the evidence base where available
- Using the Breathing, Thinking, Functioning model
Impact of breathlessness

- Poor quality of life
- Psychological morbidity
- Social isolation
- Poor symptom control
- Carer distress and exhaustion
- Increased hospital admission

“It’s terrible to see it......and you feel so helpless, so useless, so useless, I don’t know how you can help really.

Will I get much shorter of breath? Can I manage it? Is something terrible going to happen?

“He says he can’t breathe but he has enough air to yell at me”

Booth et al 2003

Invisibility of Breathlessness

- Even when severe – sitting down in consultation may not notice
- ‘Normality’ of breathlessness with COPD
- If not actively elicited, likely not to be disclosed
- Measure, assess in every patient with advanced disease


Weeks prior to death

A final common pathway?

The percentage of participants (age >70) reporting restricting breathlessness at each month during their last year of life by condition leading to death (Johnson et al. JAGS 2016)

Dyspnea Is a Better Predictor of 5-Year Survival Than Airway Obstruction in Patients With COPD* (Chest 2002, 121:1434–1440)

Breathlessness as a reason that people go to their family physician

- Breathlessness as a reason for encounter:
  - increased with age;
  - 3 X likelihood of community consultation (vs consulting room; p=0.0001)
  - 2.5 X likelihood of urgent referral to hospital (p<0.0001).
Emergency departments

- 2.7 to 9% of all presentations

- 20% of all ambulance arrivals due to acute-on-chronic breathlessness

- More likely to be admitted
  - 88% HF, 60% COPD admitted to a hospital bed. Parshall M (2001, 2006)
  - NRS (0–10); predicts admission (≥ 8/10) or discharge (< 3/10) (Saracino, 2010)
  - or serious in-hospital event (≥ 4/10, Banzett 2013)

Quality of life and the impact of chronic breathlessness

Currow DC et al. Chronic breathlessness associated with poorer physical and mental health-related quality of life (SF-12) across all adult age groups. Thorax. 2017

Adjusted (age, sex, educational attainment, smoking status, work status and smoking status) predicted mean health-related quality of life (physical and mental health components scores, possible range 0–70) by intensity of breathlessness (modified Medical Research Council (mMRC) breathlessness scale 0; 1; and ≥2).

Acute threat

- Threat to survival
- Emotional response
- Avoidance behaviour
Chronic is different

- fMRI scanning
- COPD: greater activation in the medial prefrontal cortex (emotion control and memory consolidation)
- Distorted processing of sensations: greater reliance on fear memories and expectations,
- Vicious circle of avoidance and fear.
  - (Herigstad et al Chest 2015)
Magnetoencephalographic scanning

Resting data patients and controls. Beta wave activity is higher in the MNI co-ordinates associated with perception of breathlessness. Johnson MJ et al BMJ Open 2015

Chronic is different: Jolley et al., ERJ, 2009.

- 30 patients with COPD with 26 healthy subjects matched for age, height and body mass index
- resting measures of neural respiratory drive were increased in those with COPD
  - (i.e., diaphragm electromyogram expressed as a percentage of volitional maximum [EMGdi % max])

Chronic breathlessness – a new clinical syndrome

...breathlessness that persists despite optimal treatment of the underlying pathophysiology and results in disability

Johnson MJ et al ERJ 2017 May
GOLD Guide to COPD diagnosis, management and prevention 2017

- Assessment ....based on the patient’s symptoms
- ...pharmacological therapy.....can reduce patient’s symptoms...
- ...benefit from rehabilitation......physical activity
- Assess co-morbidities...depression, anxiety, ....affect mortality and hospitalisations
- Breathlessness/Pall care services referenced


Evidence based – complex interventions for rehabilitation

- Pulmonary rehabilitation
- Cardiac rehabilitation
  - O’Connor CM et al. HF-ACTION randomized controlled trial. JAMA 2009; 301(14):1439-1450.
- Generic rehabilitation
Managing breathlessness: general principles - a complex intervention

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

Breathing, Thinking, Functioning: BTF model

1. Making sense
   - Explains breathlessness perpetuation, potential role trigger
   - Understand symptom out of keeping with disease severity

2. Motivation and mastery
   - Explains symptom relief when maximal disease management
   - Provides rationale: small change causing ‘cycle of improvement’

3. Management focus
   - Allows initial focus on predominant vicious cycle(s)

Spathis A et al. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5435098/
Management: non-drug treatment

<table>
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<tr>
<th>Breathing</th>
<th>Thinking</th>
<th>Functioning</th>
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<td>Relaxation techniques</td>
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<td>CBT techniques</td>
<td>Exercise/activity</td>
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<td>Airway clearance techniques</td>
<td>Mindfulness</td>
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<td>Singing therapy</td>
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<td>Pacing</td>
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<td>Inspiratory muscle training</td>
<td>Acupuncture</td>
<td>Nutritional supplements</td>
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<td>Chest wall vibration</td>
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<td>NMES</td>
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<td>Non-invasive ventilation</td>
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Addressing misconceptions

**Breathing**

"It is natural to think when you are feeling breathless that you need more air in. In fact this isn't the case - we know that there is plenty of air in your lungs. Try instead to lengthen your out breath, which can make your breathing more efficient and create space for your next breath."

**Thinking**

"Some people say that they're terrified that they are going to die gasping for breath. Although this is an understandable feeling, this almost never happens" (Then give a relevant explanation for a particular patient, for example "At that time, waste gases tend to build up in the blood, making people feel calm and sleepy."

**Functioning**

"Choosing to make yourself moderately breathless by being active is not harming you. In fact it builds up fitness in your muscles again and can improve your breathing and general health over weeks and months."

Breathlessness management: evidence

<table>
<thead>
<tr>
<th>Complex intervention</th>
<th>Description</th>
<th>Outcome</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nurse led OP clinic</td>
<td>119 patients Cancer RCT</td>
<td>Improved breathlessness, depression, performance status</td>
<td>Brodin BMJ 1999</td>
</tr>
<tr>
<td>Kings’ Breathlessness Support Service (AHP/medical OP/home)</td>
<td>105 patients Mixed RCT</td>
<td>Improved breathlessness mastery, and survival</td>
<td>Higginson Lancet Respiratory 2014</td>
</tr>
<tr>
<td>Cambridge Breathlessness Intervention Service (AHP/medical OP/home)</td>
<td>53 patients Cancer RCT, phase 3</td>
<td>96% benefited, reduction in distress from breathlessness</td>
<td>Faquhar BMC Medicine 2014</td>
</tr>
<tr>
<td>Three or one sessions of a breathlessness service</td>
<td>156 patients Cancer RCT, phase 4</td>
<td>No difference between one and three sessions; single session cost-effective</td>
<td>Johnson BMC Medicine 2015</td>
</tr>
</tbody>
</table>
Hand-held fan

- Facial cooling (Schwartzstein 1983)
- Altering central perception by gas temperature over nasal sensory receptors (Liss and Grant, 1988)
- Increased self-efficacy/agency in chronic illness (= increased QOL and reduced depression) (Galbraith et al. 2010)
- Mixed methods analysis of pooled data: 82% perceived some/substantial benefit (Luckett et al 2017)
- Used as part of a complex intervention – no further trials of the individual fan component needed (Johnson MJ et al JPSM 2016)

I certainly have been using it (Fan) when I get breathless, and I have a much quicker recovery than I used to ...

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

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

Airflow alters sensory attention

- Patients breathless (black)
- Recovered (grey)
- When cool air passed over face, reduction in alpha wave suppression in temporal regions

Johnson MJ et al BMJopen 2015
Thinking

• Understand triggers, context and meaning of breathlessness
• 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.)
• Information and understanding
• Misinformation and misunderstandings

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

In all these approaches remember the caregiver. Involve them in education about, and practice with the interventions. Consider their wellbeing as well as considering them only as a "care team member".

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)
Drugs – low dose morphine

- Strongest evidence in respiratory disease
- 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 reduced: standardised mean difference (SMD)
  - all studies: -0.30 (95% CI: -0.59 to -0.02)
  - steady state: -0.44 (95% CI: -0.68 to -0.19)


What about the recent Barnes et al Cochrane review?

Revised analysis of same studies Ekstrom M et al. Thorax 2017

Does a 0.8 NRS point change matter?

- Pooled data from 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
- Distribution method of measurement of MCID
  - 5.5mm detectable (small change)
  - 11.3mm (moderate change)
  - 18.2mm (large change)
- Small differences make big changes, e.g. Getting your own cup of tea. Getting to the toilet on your own...

Morphine – what dose?

• 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,
  – Just over 50% improved with 10mg per day
  – over 90% did so by 20mg per day

Currow DC et al JPSM 2011

Barriers/facilitators

• 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 Pall Med 2010)
  – Less opioiphobia than cancer patients – previous positive experiences
  – Perceived that the doctor was worried about it though
  – Faith in clinical team

Morphine- safety

• No reports of respiratory depression or opioid related hospital admission in randomised controlled trials

• Safety of Benzodiazepines and Opioids in Very Severe Respiratory Disease: A National Prospective Study.
  – N= 2249 LTOT; followed for 4 years

Canadian COPD cohort. Vozoris et al ERJ 2016

- Registry-based study: an incident opioid prescription and risk of hospitalisation or death within 30 days in those >66 years + COPD
- Propensity matched to known confounders

<table>
<thead>
<tr>
<th>Event</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency room visits for COPD/pneumonia</td>
<td>1.14, 1.00–1.29;</td>
<td>p=0.04</td>
</tr>
<tr>
<td>COPD or pneumonia-related mortality</td>
<td>2.16, 1.61–2.88;</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.76, 1.57–1.98;</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Outpatient exacerbations</td>
<td>0.88, 0.83–0.94;</td>
<td>p=0.0002</td>
</tr>
</tbody>
</table>

- In absolute terms = a 30-day mortality risk of 1.9% compared with 1.1% in people without an opioid prescription; an absolute difference of 0.8%

Points to consider – Vozoris cntd.

- "Palliative care" population were excluded (palliative physician code), but...
- Information missing
  - Clinical safety and effectiveness monitoring?
  - Why, how or at what dose the opioid was used?
  - Prevalence and severity of, or impairment due to symptoms, health and functional status?
  - NSAID use (>40% cohort had heart disease)
- Large number of sensitivity analyses with widely varying risk estimates – lessen likelihood of a causal link
- Observational studies – hard to know which is chicken and which is egg
- BUT – important message

Breathlessness – genetic predictors of response to opioid therapy


D - Cross-sectional, convenience sample. Exploratory study.
P - 1672 people on opioids for pain;
Ex- On morphine (n=588); fentanyl (n=405); oxycodone (n=429)
O - Breathlessness scores evaluated against 112 candidate single nucleotide polymorphisms (SNPs) thought to influence opioid receptors, signaling or pain modulation.
Breathlessness – genetic predictors of response to opioid therapy

Results – After adjustment 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 intense breathlessness despite being on morphine.

These findings were not seen in people on fentanyl or oxycodone.

Is this biologically plausible?

The HTR3B gene is responsible for the synthesis of the serotonergic 5-hydroxytryptamine (5HT)3B sub-type receptor.

Morphone is a weak 5HT receptor antagonist labelled the ‘M variant’ (that’s how they found >1 5HT receptor subtype)

5HT3B receptors throughout the brain except the cerebellum

Morphine is an orthosteric ligand binding site inhibitor of the 5HT3 ion channel complex, by contrast, fentanyl is not.

Therefore genetic variations in 5HT3B may variably modulate morphine-related changes in breathlessness perception whilst fentanyl has no effect.

Other drugs

- There is no evidence for, or against, 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)

- There is no evidence for a beneficial effect of buspirone for the relief of breathlessness in patients with advanced cancer (phase 3 trial) (Peoples AR et al. Support Care Cancer. 2016)

- There is emerging work for selective serotonin reuptake inhibitors – e.g. mirtazepine

Hester, aged 19. Student.

- AML initial treatment
- Stem cell transplant
- Bronchiolitis obliterans
- Breathless on walking 10 yards
- At university
- Lives with parents

Management approach

- One visit at home whilst she was home from holiday
- I saw mother, physiotherapist talked to Hester
- Breathing - Hester
- Functioning – Hester
- Thinking – Mother

Remember:

- Impact of carers
- Impact on carers
- Young people
- Those with rare diseases
George

- 58 years old
- Retired from building trade because of COPD
- Wife also a smoker with COPD
- He had had ‘panic attack’ on prom at Lowestoft with retained sputum
- Confined to home ever since
- Seen by APT – insulted – ‘imagining it, I’m a loony’
- Very tense atmosphere at home

Breathing, Thinking Functioning

- Assessment – active listening
- Breathing – use of fan, reduced use of accessory muscles
- Thinking – discussion of episode on Prom
- **Functioning**: goal walking dog round field, then pedometer programme

Chronic breathlessness

- Breathlessness isn’t just a signpost to a diagnosis
  — assess and treat in its own right
- Base assessment and management on the model of “breathing, thinking, and functioning”
- Evidence based non-drug and drug interventions can modulate the perception of breathlessness and help
  — improve self-efficacy
  — re-conditioning
- Cognitive approaches can modify the emotional response to breathlessness
- Exercise and other ways to maximise function maintain
  — quality of life,
  — reduce social isolation
  — improve breathlessness
Teaching Heart Failure Patients how to Breathe

‘There are more ways to improve symptoms than stimulation of the failing organ and the progress of disease in humans is complex and multifactorial and offers multiple approaches to amelioration.’

Coats ASJ
Lancet 1998; 351:1299-1300