Holistic management of chronic breathlessness
Miriam Johnson, Anna Spathis, Sara Booth
Oxford Advanced Course 2017
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 like being strangled while you have a big weight pushing down on your chest”

“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

- Breathlessness increases towards death in a palliative care population

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)

• Breathlessness frequency increases towards death irrespective of cause of death – even “sudden death”
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 (\(p<0.0001\)).

- Currow DC et al. Prospectively collected characteristics of adult patients, their consultations and outcomes as they report breathlessness when presenting to general practice in Australia. PLoS One. 2013 Sep 17;8(9):e74814
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
  – 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

Adjusted (age, sex, educational attainment, dwelling status, work status and smoking status) predicted mean health-related quality of life (physical and mental health components) scores (possible range 0-70) of the SF-12 by intensity of breathlessness (none – modified Medical Research Council (mMRC) breathlessness scale 0; 1; and ≥2.).
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* BMJOpen 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

• 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!**
Breathlessness

- Inefficient breathing
- Increased work of breathing
- Increased respiratory rate
- Inappropriate accessory muscle use
- Dynamic hyperinflation

Thinking

- Attention to the sensation
- Memories of past experiences
- Misconceptions and thoughts about dying
- Anxiety, feelings of panic
- Frustration, anger, low mood

Functioning

- Cardiovascular and muscular deconditioning
- Reduced activity
- Social isolation
- Reliance on help

Clinician version
May 17
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)
## Management: non-drug treatment

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<th>Functioning</th>
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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

## Complex interventions

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<th>Description</th>
<th>Outcome</th>
<th>Ref</th>
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<td>Nurse led OP clinic</td>
<td>119 patients Cancer RCT</td>
<td>Improved breathlessness, depression, performance status</td>
<td>Bredin 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>Farquhar 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>
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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) as reported by 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)

- Rocker G et al. JOURNAL OF PALLIATIVE MEDICINE Volume 10, Number 3, 2007
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? Ekstrom M et al. Thorax 2017

Revised analysis of same studies

1. Barnes et al did not take into account the crossover design despite there being standard ways to do this. Therefore significant loss of precision.
2. Added an additional criterion for risk of bias which meant the good quality design studies with adequate power were rendered high risk of bias and poor quality evidence.
3. When re-analyzed to account for crossover data, opioids decreased breathlessness (SMD −0.32; −0.18 to −0.47; I²=44.8%) representing a clinically meaningful reduction of 0.8 points (0–10 numerical rating scale), [Barnes: -0.28 (-0.05 to -0.05)]
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
  – No associated excess mortality or hospitalisation if daily dose 30mg morphine equivalents or less

Ekström M P et al. BMJ 2014;348:bmj.g445
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>
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<tr>
<th>Event</th>
<th>HR (95% CI) p value</th>
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<td>emergency room visits for COPD /pneumonia</td>
<td>HR 1.14, 1.00–1.29; p=0.04</td>
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<tr>
<td>COPD or pneumonia-related mortality</td>
<td>HR 2.16, 1.61–2.88; p&lt;0.0001</td>
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<tr>
<td>all-cause mortality</td>
<td>HR 1.76, 1.57–1.98; p&lt;0.0001</td>
</tr>
<tr>
<td>outpatient exacerbations</td>
<td>HR 0.88, 0.83–0.94; p=0.0002</td>
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- 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

  Morphine has a known safety profile and should be prescribed i) for the right patient, ii) with due care in monitoring.

  This is the same principle for prescribing beta blockers, ACE-inhibitors, beta agonists, anti-diabetic medication, digoxin, ...
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 (=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.

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

5HT\(_{3B}\) receptors throughout the brain except the cerebellum

Morphine is an orthosteric ligand binding site inhibitor of the 5HT\(_3\) ion channel complex, by contrast, fentanyl is not.

Therefore genetic variations in 5HT\(_{3B}\) 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

Ted, aged 76. Retired fireman.

- NSCLC stage IV
- COPD
- LVSD due to IHD
- Lives in 1st floor flat with no stairs, but beautiful view
- Son and daughter live in town
- Wife Betty has arthritis but otherwise fit for her 72 years
- Recently back home again following a emergency department attendance for severe breathlessness which settled quickly
Management approach

• Review Mx of multi-morbidities

• Understand the story of attendance
  – was there a trigger?
  – What tipped him into crisis?
  – Who is involved in his care, and who was part of the decision to go to the ED?

• What breathlessness management strategies does he employ? Which has he tried?

• How well is he functioning?
  – Physically?
  – Psychologically?
  – Within the family?
What did we do? Disease targeted

- BP low – feels dreadful, but compensated cardiac status: reduce dose of ACEI
- Check his HB – he has had some haemoptysis
- Consider palliative RT for haemoptysis
- On correct inhalers, and technique good
- Single session breathlessness service including fan
- Breathlessness crisis plan
- Education re role of exercise
What did we do?- breathlessness targeted

• Understanding triggers for panic
  – Memory of smoke inhalation as part of his work
  – Haemoptysis is frightening – reminded him of his father’s death
  – Breathlessness worse = the cancer is “galloping”
  – “forgot” that his usual pattern was to settle after a few minutes

• Discussion about coping strategies
  – Ways to maintain role in family
  – Ways to maintain social contact
  – Ways to “live as well as you can for as long as you can”
What did we do? - breathlessness targeted

- He had very little pain
- Started on 10mg BD modified release morphine,
  - with a laxative,
  - warned about nausea and the need to access anti-emetics
- Involved Betty in the discussions and shown how he should use the fan and exercises
- Communicate with rest of health care team across both primary and secondary care settings
- Identify key member of team to be primary liaison person
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