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Longer-term opioid-related improvement in breathlessness

- postulated mechanisms

ST CATHERINE'S HOSPICE

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Longer-term opioid-related improvement in breathlessness – postulated mechanisms

- Morphine is beneficial for the relief of breathlessness
  - 1 cochrane review (Jennings AL et al Thorax 2001)
  - 3 systematic reviews (Ben-Aharon I et al J Clin Oncol 2008; Booth et al Nat Clin Pract Oncol 2008; Viola R et al Support Care Cancer 2008)
  - Powered RCT (Abernethy AP et al BMJ 2003)
  - Pilot RCT (Johnson MJ et al EJHF 2002)
  - Dose titration and pharmacovigilance study (Currow et al 2011)
- A powered RCT in people with heart failure (Oxberry SG et al EJHF 2011) comparing morphine vs oxycodone vs placebo
  - All arms improved, none better than the others

3 month open label follow up of patients completing this RCT

- 33/35 patients completing RCT agreed for FU
- 13 continued open label opioid; 20 did not
- Breathlessness intensity measures combined using principal component analysis for the primary analysis and groups compared using analysis of covariance.

Principal component analysis

- to simplify data across multiple variables by collapsing the variables to fewer composite variables
- the composite variables
  - are reductions based on the results of the principal component analysis
  - identify the relative correlation with the outcome of interest
- principal component analysis conducted for:
  - NRS (worst/average over 24 hours) mBorg (worst/average over 24 hours)
  - Global impression of change in breathlessness
- PCA yielded only one meaningful component, which accounted for 74% of the total variance.

Results at 3 months

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Breathlessness severity variable	Chose to take opioids (n=13)		Chose not to take opioids (n=20)		Significance (analysis of covariance except global impression of change, t test)
	Baseline Mean (SD)	Three months Mean (SD)	Baseline Mean (SD)	Three months Mean (SD)	
Principal component (lower scores represent less breathlessness)	0.18 (1.80)	−2.05 (2.02)	−0.12 (1.70)	−0.26 (1.99)	0.017
NRS Average *	5.31 (1.97)	3.31 (2.21)	4.95 (1.82)	4.95 (1.99)	0.033
NRS Worst *	5.23 (1.54)	4.69 (2.59)	7.20 (1.61)	7.05 (2.01)	0.006
Borg Average *	3.23 (1.30)	1.92 (1.12)	2.80 (1.46)	2.88 (1.59)	0.087
Borg Worst*	4.46 (2.15)	2.65 (1.65)	4.30 (2.11)	3.80 (2.28)	0.12
Global Impression of Change (negative scores mean a change for the worse)	Not applicable	2.62 (3.36)	Not applicable	−0.65 (1.76)	0.0009

Results at 3 months

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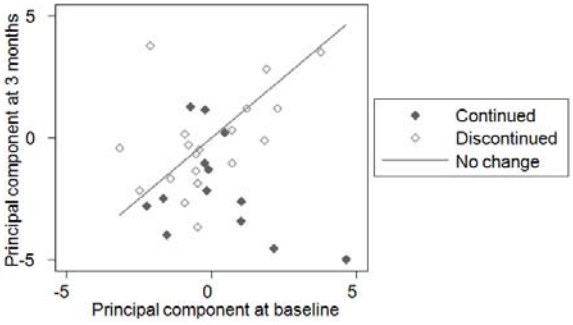
- SF-12 improved opioid > non-opioid (physical component: p = 0.014).
- cardiorespiratory variables were unchanged.

Principal component summary of breathlessness variables; three month values plotted against baseline values. Low values represent less breathlessness.



Hypothesis: full opioid related benefit may not be seen in the short term

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- Possible mechanisms
  - improved exercise tolerance with increased activity over time? (any aetiology)
    - Via peripheral mechanisms
    - Via central mechanisms
  - opioid receptor activation inhibits sympathetic drive by reducing intracellular cAMP (Wong and Shan 2001) – could exogenous opioids modify both breathlessness and sympathetic activation? (increased sympathetic drive seen in HF)