CareSearch Project Research Studies Register: Registration Proforma	0153

Study Title: A randomised double-blind multi-site parallel arm controlled trial to assess relief of refractory breathlessness comparing fixed doses of morphine and placebo.

Brief description of the study: Background: Breathlessness continues to be a major clinical problem for many people with advanced progressive illnesses such as chronic obstructive pulmonary disease, end-stage cardiac failure, and cancer, even when they are receiving the best treatment for their underlying disease. There are phase II/III data and one meta-analysis which support the use of morphine in this setting, but further good phase III data are needed in order to ensure that this is a well tolerated and effective intervention suitable for a broad range of people with refractory breathlessness. It is also important to establish that the overall net benefit outweighs any toxicity encountered. Further, a particular concern to many clinicians is the theoretical risk that opioids may cause respiratory depression. In steady state, at the relatively low regular doses proposed, there are no data to support this concern, but this study will specifically address this question through careful collection of non-invasive measures of respiratory function regularly throughout the study including end-tidal carbon dioxide at the beginning and the end of the study. Objectives: Among participants with refractory breathlessness (that is where all underlying reversible are being treated and breathlessness persists): 1) To compare the efficacy for relieving the sensation of dyspnoea, level of function, safety and quality of life (QOL) of sustained release morphine with placebo2) To identify clinical and pharmacogenomic parameters that predict which individuals will achieve the greatest benefit from the interventions and establish any blinded participant preference. Secondary objectives focus on the impact of the interventions on improving quality of life, adverse effects, function, use of breakthrough opioids and clinical predictors of benefit. Study design: This is a phase III, multi-site, randomised double-blind parallel arm fixed dose controlled trial studying treatment approaches for the palliative relief of breathlessness in participants with refractory dyspnoea. Participants will be randomised to fixed dose identical-appearing sustained release morphine (20 mg every 24 hours), or placebo for one week. The intervention period will run for 7 days; participants will receive study interventions at target doses and blinded therapy for constipation with each active arm together with identical appearing placebo for constipation for the placebo arm. Study settings: Palliative Care Clinical Studies Collaborative (PaCCSC) Phase 3 sites (Flinders Medical Centre SA, Repatriation General Hospital SA, Braeside Hospital, NSW, St Vincent's / Sacred Heart NSW, Calvary Mater Newcastle, NSW, Mater Health Services, Qld, The Prince Charles Hospital, Qld, Calvary Health Care Kogarah, NSW, St Vincents Hospital, Melbourne, Vic, Royal Melbourne Hospital, Vic, Barwon Health, Vic, Lyell McEwin Hospital, SA, and the Austin Hospital, Melbourne (separately funded by an NHMRC grant). Participants: People with breathlessness of a level of 2 or higher on the Modified Medical Research Council (mMRC) Dyspnoea Scale, despite optimal treatment of the underlying causes of this breathlessness. Study interventions: Every morning, participants will take three capsules (one Kapanol 20mg or placebo, and two docusate with senna or placebo). This will occur without titration and participants will have one week of treatment

allocated in a double-blind random way at the beginning of the study. Participants will not have been on regular opioids at a dose higher than the study dose for the previous week. 'As needed' open label docusate with senna will also be provided to all study participants. Given evidence favouring opioids, all participants will have access to 2.5mg of immediate release morphine solution to be taken orally on an 'as needed' basis through the study. Definition of response: A response will be defined as a 15% reduction in the sensation of breathlessness over baseline breathlessness scores. Primary endpoint: Breathlessness in the last 24 hours averaged over the last 3 days of study is the primary end-point. The primary assessment is the twice daily diary filled out by participants. Potential side effects will be monitored in the daily diary across the whole study period. Analysis: Longitudinal repeated measures mixed models with unstructured covariance matrices, two-sample t tests, and multivariable regression models will be used. Sample size: Data on 235 people will be required in order to complete the study with adequate power for the least powered arm.

Study Methodology: (Please mark with an x which type of study methodology)

	Epidemiology
	Health Services / Health Economics / Quality Improvement
	Qualitative, Observational or Descriptive
	Mixed Method
	Systematic Review
X	Intervention: RCT
	Intervention: Comparative or cohort study
	Intervention: Case series

Project details:

Funding source (Optional): Australian Government Department of Health

Has the study received ethics approval?	**X**	Yes		No		Not applicable

Project starting date: Feb 2010

Project completion date: July 2015

Multi site:	**X**	Yes		No		Not applicable

Researchers

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Associated publications / reports:
Topics (Admin only) Dyspnoea, Drug trial