CareSearch Project Research Studies Register: Registration Proforma	0155

Study Title: Randomised control trial of oral risperidone, oral haloperidol, and oral placebo with rescue subcutaneous midazolam in the management of delirium in palliative care inpatients.

Brief description of the study: Background Delirium is prevalent in patients with advanced cancer and in the palliative care setting, and is associated with significant and distressing symptomatology and poor prognosis. Antipsychotics are considered by most clinicians as first line pharmacotherapeutic agents for delirium despite limited level 2 evidence for management of delirium in any health care setting, including palliative care. The few studies that exist explore post treatment efficacy in relation to total delirium score reduction, and do not guide management of target symptomatology. There has been no systematic evaluation of toxicity profile in relation to delirium management with typical or atypical antipsychotics, in particular extrapyramidal toxicity and degree of sedation. There is need for randomized control trial evidence of the efficacy of antipsychotics to control targeted delirium symptoms, and also to consider broader implications on caregiver and patient distress. Study design A randomised double blind placebo controlled phase III study to compare the effectiveness and toxicity of oral risperidone, oral haloperidol, and oral placebo with rescue subcutaneous midazolam in the management of palliative care patients with "Diagnostic and Statistical Manual of Mental Disorders – IV edition revised" (DSM IV – R) defined Delirium. Objectives Primary Objective: To compare the efficacy of oral Risperidone solution and control (oral placebo solution with subcutaneous midazolam rescue). Secondary Objectives: To compare oral Haloperidol solution and control; and oral Risperidone solution and oral haloperidol solution in control of targeted delirium symptoms at 72 hours from treatment commencement. Treatment schedule Commencing doses will be a loading dose of 0.5mg ((0.25mg in > 65yrs),, then 0.5 mg bd (0.25mg bd in > 65 yrs) in both haloperidol and risperidone arms, with 12 hourly increments based on target delirium symptom(s) score. Maximum dose will be 4mg, and 2 mg in those > 65 years. Rescue protocol commences at 2.5mg subcutaneously midazolam 2 hourly based on targeted delirium symptom(s) score, with titration protocol if ineffective. Assessments Delirium will be assessed using Nursing Delirium Screening Scale and Memorial Delirium Assessment Scale. Comorbidity burden, medication, and prior cognitive impairment will be assessed. Toxicity will be measured using validated scales - Extrapyramidal Symptom Rating Scale and Richmond Agitation Sedation Scale. Patient, caregiver and nurse rated distress due to delirium symptoms will be measured. Primary endpoint Change in sum of scores on Nursing Delirium screening scale (NuDesc) items 2 (inappropriate behaviour), 3 (inappropriate communication), and 4 (illusions/hallucinations) from baseline and follow-up (on day 3), where baseline is the average of the eligibility score on entry to the trial and the score obtained before the first dose is given, and follow up is the average of the last morning and evening scores on the third day. Clinical response A one-unit change between baseline and follow up scores. Analysis: A total sample size of 110 patients (55 risperidone, 55 control) will provide 80% power to detect a difference in change of NuDesc score of 1 unit

assuming a baseline Standard deviation of 1.92 units, and a correlation of at least 50% between baseline and follow-up scores. The change in sum of NuDesc scores (item 2, 3 and 4) between baseline and follow-up between arms will be evaluated as the group effect (coded 0/1) from the regression of the average of follow up scores on the average of baseline scores and group. Intention to treat analysis will be used. Economic analysis The economic evaluation will estimate incremental costs (resource use); patient effects; and caregiver and health professional consequences in comparisons of Risperidone, Haloperidol and placebo from patient level data collected over 28 days of follow up. Patient level resource use data collected to inform for this analysis will include: days spent in hospital (index admission and readmissions), in hospital use of nursing assistants, non hospital institutional bed days, medication use, general practitioner visits, home care palliative care team review visits. Data on effects and consequences collected to inform this analysis will include patient efficacy (Nursing delirium scale scores), toxicity, and medical complications and caregiver and health professional impact/distress.

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: August 2008

Project completion date: August 2014

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

Researchers

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