CareSearch Project Research Studies Register: Registration Proforma	0071

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 1mg, then 0.5 mg bd 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.

Definition of response: 2 point or greater reduction in sum of scores on the Nursing Delirium Screening Scale item 2 (inappropriate behaviour), 3 (inappropriate communication), and 4 (illusions/hallucinations) at 72 hours.

Primary endpoint: Sum of scores on Nursing Delirium screening scale items 2 (inappropriate behaviour), 3 (inappropriate communication), and 4 (illusions/hallucinations) at 72 hours.

Analysis: A total sample size of 165 patients (55 risperidone, 55 haloperidol, 55 control) will provide 80% power, at a 2-tailed type I error of 0.05, to detect a difference of 0.55 SD unit between any two treatment means. The sum of NuDesc scores (item 2, 3 and 4) at 72 hours will be compared by analysis of variance. The corresponding score at baseline will be used as a covariate. 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 of Health and Ageing

Has the study received ethics approval?	x	Yes		No		Not applicable

Project starting date: 15 January 2008

Project completion date: 30 June 2010

Multi site:	x	Yes		No		Not applicable

RESEARCHERS

Principal Investigator (name)	Dr Meera Agar
Contact Details	Braeside Hospital , Locked bag 82, Wetherill Park, NSW 2164 Phone: + 61-2-9616 8654, Fax: + 61-2-9616 8657 email: Meera.agar@sswahs.nsw.gov.au
Investigator B (Name)	A/Professor Brian Draper
Investigator C (Name)	A/Professor Gideon Caplan
Investigator D (Name)	Dr Mark Hill
Investigator E (Name)	Ms Tania Shelby-James

Associated publications / reports: None

Topics (Admin only) Delirium, Drug trials