

## **Appendix D: Included studies: Pharmacological Risk Factors**

<b>Study details</b>	<b>Patient details</b>	<b>Factors adjusted for</b>	<b>Anaesthesia/surgery</b>	<b>Further details</b>
Agostini 2001; prospective cohort study; country USA; total number of patients: 426	Age: 80 years (73.2 to 86) Cognitive impairment: MMSE at baseline ~23 Sensory impairment: no details Polypharmacy: Antidepressants, antipsychotics, anxiolytic, sedative, and hypnotic drugs. Average number of medications prior to admission about 6.	Age, gender, delirium risk	Ward: Other Type of anaesthesia: not stated; type of surgery: unclear/not stated	Inclusion/exclusion: Inclusion criteria 70 years or older with no baseline delirium. Exclusion criteria - profound dementia, hospital discharge within 48 hours of admission, non-english speakers.  Patients admitted to a non-intensive care ward of a teaching hospital.
Beaussier 2006; RCT study; country Unclear France/Switzerland; total number of patients: 59	Age: 77.5 years (72 to 83) Cognitive impairment: no details Sensory impairment: no details Polypharmacy: Premedicated with oral hydroxyzine 1mg/kg. Post-op paracetamol 1 gram given to patients	not applicable	Ward: Surgical Type of anaesthesia: general; type of surgery: Colon resection surgery	Inclusion/exclusion: Inclusion criteria cancer of the left colon or rectum with surgical indication for resection in patients >70 years. Excluded:Body mass index > 30kg/m /sq, inflammatory bowel disease, contraindications to intrathecal morphine administration, preoperative m.  Postoperative colorectal surgery. General anaesthesia IV thiopental 3-5mg/kg and sufentanil 0.2-0.3 micrograms/kg and atracurium 0.5 mg/kg to facilitate intubation.

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Centorrino 2003; retrospective cohort study; country USA; total number of patients: 139	Age: 40.8 years(28.7 to 54.9) Cognitive impairment: no details Sensory impairment: no details Polypharmacy: Medications at admission- no details Comorbidities: 65 patients also had comorbidities, no further details	Bivariate analysis of association of factors with the presence or absence of delirium; followed by multivariate logistic regression analysis of factors identified. Factors associated with delirium: anticholinergic medication, clinical responder, age, hospitalised>20 days, any antipsychotic, CNS-agent, anticonvulsants, any mood stabiliser, clozapine dose >250mg/day, tricyclic antidepressants, benzodiazepines, serotonin reuptake inhibitors, women, lithium, any anti-depressant	Ward: Mental Health Type of anaesthesia: not stated; type of surgery: unclear/not stated	Inclusion/exclusion: Consecutive hospitalised patients given clozapine of all admissions during seven months that was sampled..  Computerised pharmacy records used to identify incidences of delirium
Christe 2000; RCT study; country Switzerland; total number of patients: 65	Age: median:84 years (63 to 98 ) Cognitive impairment: MMSE Sensory impairment: no details Polypharmacy: Lidocaine spray used as premedication; supplemental oxygen given to patients	MMSE score <21	Ward: Medical Type of anaesthesia: regional; type of surgery: Gastro-intestinal endoscopy	Inclusion/exclusion: Excluded - unwillingness to participate in the study, Mini Mental State score <20, or myasthenia gravis..  Geriatric inpatients requiring upper gastrointestinal endoscopy.Median age 85 years. Intravenous catheter used with all patients and all given oxygen via nasal catheter. 94 patients evaluated and 65 included in the study.

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Dubois 2001; prospective cohort study; country Canada; total number of patients: 216	Age: 64.8 years ( 49.3 to 79.7) Cognitive impairment: Sensory impairment: visual or hearing impairment not reported Polypharmacy: Pts received benzodiazepines, propofol, lorazepam, morphine, fentanyl, meperidine, steroids Comorbidities: Hypertension, COPD	hypertension, smoking history, bilirubin level, use of epidural, morphine; UV:COPD,alcohol abuse, sodium level, glucose level, lorazepam, rooms without windows, rooms with window	Ward: ICU Type of anaesthesia: mixed general/regional groups; type of surgery: Mixed	Inclusion/exclusion: All consecutive patients aged 18 or more, admitted for 24h, deemed likely to survive 24h; exclusion criteria not reported.
Foy 1995; prospective cohort study; country Australia; total number of patients: 418	Age: 70.2 years( 59 to 88) Cognitive impairment: Assessed with MMSE; Sensory impairment: no details Polypharmacy: Medications at admission- no details for polypharmacy	benzodiazepiones in urine, hypoxia, previous medical diagnosis of CNS & mental disorders, alcohol consumptions >40mg/day, sepsis, admission diagnosis, cerebrovascular accident, benzodizepine use in past 5 days, dehydration, neuroleptics or rycyclics in past 5 days	Ward: Mixed: Medical/Surgical Type of anaesthesia: not stated; type of surgery: likely to be mixed	Inclusion/exclusion: Patients in need of resuscitation, or were comatose or semi-comatose were excluded, as were patients admitted for day ony procedures or for terminal cancer, and those blind, aphasic or non-english speaking..  Included: Inpatients aged 60 years or over with normal cognitive function on admission to hospital

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Han 2001; prospective cohort study; country Canada; total number of patients: 278	Age: 83.4 years (76.1 to 90.7) Cognitive impairment: 180/278 pts w/dementia; Assessed with ICODE Sensory impairment: 19.8% with visual or hearing impairments; Polypharmacy: atypical antipsychotics, anticholinergics, benzodiazepines	age, length of follow-up, serum albumin level, medication measures, dementia, baseline Delirium Index score, visual or hearing impairment, delirium type (prevalent; incident) and study group (trial: intervention, control)	Ward: Medical	Inclusion/exclusion: Consecutive pts 65y or older admitted from the ED to the medical or geriatric services; Excl: admitted on a Fri or Sat; diagnosed as having stroke or terminal illness ; under intensive care or cardiac monitoring for >48h; not speak or understand Eng/French.
Herrick 1996; RCT study; country Canada; total number of patients: 136	Age: 72 years (65 to 85) Cognitive impairment: MMSE scores revealed reduced cognitive function post-operatively Sensory impairment: no details Polypharmacy: antiemetics		Ward: Surgical Type of anaesthesia: mixed; type of surgery: orthopedic surgery	Inclusion/exclusion: Included patients 65 years of older undergoing elective hip or knee arthroplasty..  Patient Controlled Analgesia fentanyl compared with PCA morphine . Originally 136 randomised but only 96 studied.

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Holroyd 1994; retrospective cohort study; country USA; total number of patients: 114	Age: 71.9 years (65 to 92) Cognitive impairment: MMSE mean score 25.1 Sensory impairment: no details Polypharmacy: Medications at admission- no details; psychotropic drugs used in the past	no details	Ward: --- Type of anaesthesia: not stated; type of surgery: unclear/not stated	Inclusion/exclusion: Consecutive charts reviewed covering 14 year- period. All patients over the age of 65 years who had ever been prescribed lithium at any point during outpatient therapy..  Elderly outpatients with mood disorders treated with lithium for an average of 7.5 years
Kim 1996; RCT study; country USA; total number of patients: 127	Age: 66 years (24 to 86) Cognitive impairment: MMSE Sensory impairment: no details Polypharmacy: Medications at admission- no details for polypharmacy	Age and length of hospital stay as covariates were introduced into the MANOVA model to control for their effects on the MMSE scores. Logistic regression procedures were used to control for age and other effects of the incidence of delirium. Surgical variable were recorded to assess their possible confounding natures.	Ward: Surgical Type of anaesthesia: not stated; type of surgery: cardiac surgery	Inclusion/exclusion: Excluded if taking H-2 antagonists preoperatively, or required warfarin, lidocaine, phenytoin or theophylline.  Cimetidine compared with ranitidine. Both prescribed following cardiac surgery for prophylaxis gastric stress bleeding

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Leung 2006; RCT study; country USA; total number of patients: 228	Age: 74 years( 65 to 95) Cognitive impairment: TICS Sensory impairment: no details Polypharmacy: benzodiazepines; pca analgesia, and oral opioids	Intraoperative anaesthetic management: patients were randomised to either nitrous oxide with oxygen versus oxygen alone.	Ward: Surgical Type of anaesthesia: general; type of surgery: likely to be mixed	Inclusion/exclusion: Inclusion criteria: men & women ≥65 years, undergoing non-cardiac surgery. Exclusion criteria: unable to complete neuropsychological testing.  Pre-medicated was limited to fentanyl up to 2 µg /kg IV. Additional morphine or fentanyl allowed . After operation PCA was used for pain control.
Morrison 2003; prospective cohort study; country USA; total number of patients: 541	Age: <70: 9%; 70 to 79: 26%; 80+: 65% Cognitive impairment: 55% [297/541] were cognitively impaired; based on diagnosis or Hx of memory impairment or a dementing illness or made one or more error in 4-item test Sensory impairment: no details Polypharmacy: benzodiazepines or other sedatives and hypnotics, opioids (including meperidine)	Age, gender (women), residence in nursing home, cognitive impairment, FIM score (2 levels), RAND score (2 levels), Abnormal BP, Abnormal heart rhythm, chest pain, medical complication, morphine (2 levels), meperidine	Ward: Surgical	Inclusion/exclusion: Patients admitted with intertrochanteric or femoral neck fracture without evidence of delirium. Patients who were found to be delirious at initial interview (within 48h after admission) were excluded.

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Nitschke 1996; RCT study; country USA; total number of patients: 92	Age: 66.6 years (65 to 69) Cognitive impairment: MMSE administered 1 day before surgery and 1-5 days after op Sensory impairment: no details Polypharmacy: Medications at admission- no details	not applicable	Ward: Surgical Type of anaesthesia: mixed; type of surgery: Colon resection surgery	Inclusion/exclusion: Excluded: severe chronic obstructive pulmonary disease, severe cardiac disease, allergy to morphine, ketorolac, non-steroidal anti-inflammatory drugs, pregnancy, age younger than 18 years.  PCA morphine vs. IM morphine vs. IM Ketorolac. MMSE used to assess post-op confusion. Five ketorolac patients switched to a different analgesic and one IM morphine changed analgesics
Pandharipande 2006; prospective cohort study; country USA; total number of patients: 198	Age: 55.5 years (38.5 to 72.5) Cognitive impairment: Blessed Dementia Rating score: 0.2 (SD 0.7); range: 0 to 17 Sensory impairment: 58% visual & 16% hearing impairment Polypharmacy: antipsychotics,anticholinergics, opioids, sedatives	age, gender, visual and hearing deficits, history of dementia, depression, severity of illness [modified APACHE II], sepsis, history of neurologic disease (stroke, epilepsy, other CNS), baseline hematocrit, daily glucose concentration, cognitive status at previous 24 h and medications [lorazepam, midazolam, fentanyl, morphine, propofol]	Ward: ICU	Inclusion/exclusion: Adult, mechanically ventilated patient admitted to the medical or coronary ICUs. Exclusion criteria included baseline neurologic diseases that would confound the evaluation of delirium..  Admitting diagnoses: sepsis/acute respiratory distress, pneumonia, MI/CF, COPD, GI bleeding, drug overdose, hepatic or renal failure, malignancy, other

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Papaioannou 2005; RCT study; country Greece; total number of patients: 47	Age: median: 68 years Cognitive impairment: MMSE Sensory impairment: no details Polypharmacy: Medications at admission		Ward: Surgical Type of anaesthesia: mixed general/regional/co mbined; type of surgery: likely to be mixed	Inclusion/exclusion: excluded illiteracy, severe auditory or visual disturbances, central nervous system disorders, alcoholism or drug dependence, treatment with tranquillisers, or antidepressants, dementia, parkinson's disease.
Pisani 2009; prospective cohort study; country USA; total number of patients: 304	Age: 75 years ( 67 to 83) Cognitive impairment: baseline dementia assessed using IQCODE Sensory impairment: no details Polypharmacy: benzodiazepine or opioid (81%); medium to high potency ACH (32%), haloperidol (32%), steroid use (52%) Comorbidities: respiratory disease (50%), GI haemorrhage (17%), sepsis (16%), neurological disorder (2%), other (15%)	MV: medications (benzodiazepine or opioid use; medium to high potency ACH use; haloperidol use anytime during ICU stay; steroid use anytime during ICU stay), impairment in ADL, depression, dementia, admitting diagnosis of respiratory disease, APACHE II(minus Glasgow Coma Scale), alanine aminotransferase>40 U/l	Ward: ICU	Inclusion/exclusion: Consecutive patients 60 years or older admitted to a medical ICU from Sept 2002 to Sept 2004; patients were excluded if proxy was unavailable to provide info, they transferred from another ICU, admission less than 24 hrs, or they were non-English speaking.

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Shulman 2005; retrospective cohort study; country Canada; total number of patients: 10230	Age: 74.7 years (67.8 to 81.5) Cognitive impairment: no details Sensory impairment: Hearing impairment and visual impairment at baseline Polypharmacy: Medications at admission- no details	Controlled for age, comorbidity, visual impairment and hearing impairment, no further details.	Ward: Unclear/Not stated	Inclusion/exclusion: Ontarians who were over 60 years with mood disorders, and were newly dispensed 1 of the 3 drugs; Excluded previous diagnosis of dementia, epilepsy, prior history of delirium, brain tumour, schizophrenia..  Lithium, valporate and anticholinergic agents