APPENDIX A. SEARCH STRATEGIES

Delirium screening and diagnosis

Database: Ovid MEDLINE(R)
Search Strategy:

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1 confusion.mp. or exp Confusion/
2 exp Delirium/ or delirium.mp.
3 deliri$.tw.
4 (NEECHAM or "Neelon and Champagne Confusion Scale").tw.
5 (MMSE or mini-mental stat$ exam$).tw.
6 or/1-5
7 sensitiv$.mp.
8 predictive value$.mp.
9 accurac$.tw.
10 or/7-9
11 6 and 10
12 limit 11 to english language
13 mass screening.mp. or exp Mass Screening/
14 diagnosis.mp. or exp Diagnosis/
15 13 or 14
16 12 and 15

Delirium prevention

Database: Ovid MEDLINE(R) <1950 to November Week 2 2010>
Search Strategy:

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1 exp Delirium/
2 deliri*.mp.
3 exp Confusion/ or acute confusion.mp.
4 acute organic psychosyndrome.mp.
5 acute brain syndrome.mp.
6 metabolic encephalopathy.mp.
7 acute psycho-organic syndrome.mp.
8 clouded state.mp.
9 clouding of consciousness.mp.
10 exogenous psychosis.mp.
11 toxic psychosis.mp.
12 toxic confusion.mp.
13 or/1-12
14 exp Primary Prevention/
15 prevent*.mp.
16 avoid*.mp.
17 or/14-16

18 13 and 17
19 exp Alcohol Withdrawal Delirium/
20 delirium tremens.ti.
21 19 or 20
22 18 not 21
23 exp animals/ not humans.sh.
24 22 not 23
25 limit 24 to english language
26 limit 25 to yr="1966 -Current"

APPENDIX B. STUDY SELECTION FORM

First Author			**Eligible Study? Y N** **If N, what # below? 1 2 3 4 5 6 7 8 9 10 11**			**Screening? Y N**		**Prevention? Y N**		**Diagnosis? Y N**	
Title of Study					**Country**		**Journal**			**Year**	
Study Design	**Cohort**	**Cross-sectional**		**Case-control**		**RCT**		**Non-RCT**			**Review/Meta-analysis**
Sample	**Sample size**	**Inclusion Criteria**		**Exclusion Criteria**			**Veteran?**		**Elderly 60+?**		**ICU?**
							Y N		**Y N**		**Y N**
							Gender?		**Age Range?**		**Ethnicity?**
							M F				
Screening, Diagnostic Tools or Approaches Used		**CAM**	**Others/Details:**							**Prevention strategies:**	
		CAM-ICU									**Nursing interventions**
		MMSE									**Hydration**
		ICDSC									**Music**
		DRS									**Medications**
		MDAS									
		DSM-IV									
Findings/ Outcomes		**Diagnostic accuracy**	**Others/Details:**								
		Delirium incidence									
		Delirium duration/severity									
		Length of stay									
		Use of rescue meds									
		Discharge to rehab/NH									
		Health economics									
Exclusion Criteria (*=does not apply to Prevention Studies)	**1**	**2**	**3**	**4**	**5***	**6***	**7***	**8**	**9**	**10**	**11**
	Non-English	<16 yo	Alcohol-related	Not hospitalized	No reference standard	Reference standard not done by specialist	Same person did test/ reference standard	Case series/ report, letter, or editorial	Not delirium	No outcomes of interest	Not screening, prevention, diagnosis

APPENDIX C. PEER REVIEW COMMENTS/AUTHOR RESPONSES

REVIEWER COMMENT	RESPONSE
1. Are the objectives, scope, and methods for this review clearly described?	
Yes. The incidence of delirium is a significant complication of hospitalization that warrants further review. The ability for identification and prevention of delirium in medically ill patients is a current need. The objectives of this study were clearly stated and it appears that a large data base of research was examined to address the key questions posed by this review.	
Yes	
Yes	
Yes	
Yes. I think Key Question #1 includes multiple disparate elements "effectiveness" is really answered by question #3 diagnostic accuracy, as is vary in results. In the summary, only does screening improve clinical outcomes is answered.	Effectiveness is not adequately addressed by KQ3 "diagnostic accuracy". While there was no direct evidence of the effectiveness and harms of screening for delirium we have described in the KQ1 results section the pieces of chain of evidence that would need to be addressed for indirect evidence of effectiveness.
Yes	
2. Is there any indication of bias in our synthesis of the evidence?	
No.	
No	
No	
No	
No. Honestly, I have a sense of bias, but it is hard to identify the source. I am a little worried that your questions are so narrow that a naïve reader will say… well, there is nothing new here since 1970. When in fact, it is pretty clear that delirium is associated with mortality, that some drugs are used more commonly in patients who develop delirium, that haldol can attenuate the consequences of delirium, that benzodiazepines in patients at risk should be avoided……..	The scope of this report was not to assess all pharmacologic interventions that increase a person's risk of delirium. However, we have added categories of medications widely recognized to be associated with delirium. We also have described that delirium is associated with mortality.
No	
3. Are there any <u>published</u> or <u>unpublished</u> studies that we may have overlooked?	
No. Not to my knowledge.	
No. This is an amazing compendium of information, and I have little to add, especially given comment about authors' awareness of, and plans to include information from, June 2011 article in Annals of Internal Medicine.	Thank you
No	
There are pending publications from 2 studies (Boustani and Marcantonio) on cholinesterase inhibitors and their role in delirium prevention.	Our inclusion criteria required articles be published in peer review manuscripts.
I don't know the literature sufficiently to know.	
I am not aware of any studies that were overlooked.	

REVIEWER COMMENT	RESPONSE
4. Are there any clinical performance measures, programs, quality improvement measures, patient care services, or conferences that will be directly affected by this report? If so, please provide detail.	Thank you – we will share these suggestions with the people responsible for dissemination of the report.
Presently OQP reviews inpatient records for evidence of elevated risk for delirium. Because these efforts are still in a relatively early stage, not much attention has been drawn to them—but as the data and the outcome correlations become more robust, educational efforts can be undertaken to support use of the QI and thereby, to enhance quality of inpt. care. Some of these data were presented at a recent VA conference (EES) in Indianapolis that focused on safety enhancement in different health delivery settings. In the two preceding years (2009, 2010), national conferences concerning delirium prevention, recognition, and management were also held in Boston and Baltimore. Plans are just beginning for a "Emergency Rooms and the Elderly Veteran" conference for Spring 2012. OQP is also examining a proposal from GEC to adapt a number of the "Assessing Care of Vulnerable Elderly" QIs to VA—several of these have to do with documenting mental status upon hospital admission in order to have a baseline against which subsequent mental status may be compared. The Office of Geriatrics and Extended Care currently supports several demonstration pilots (about to embark on their 3rd years of funding) specifically directed to delirium prevention in different settings: in San Francisco, an Acute Care for the Elderly unit; in Connecticut, a home-based presurgical assessment followed by post-discharge transition management; in Boston, a "Delirium Toolbox" for reducing risk factors in recent admissions with demonstrated elevated risk for delirium; in Durham, a caregiver education program to assist with behaviors associated with cognitive decline; in Indianapolis, a transition management approach that begins during an inpatient stay; and in New Orleans, Portland, Boise, and Honolulu, a "Hospital at Home" that provides an inpatient level of care in the home for targeted diagnoses, with complete avoidance of delirium. There is a national Dementia Steering Committee that developed a strategic plan and has educational, clinical, and research activities underway. Because dementia is one of the most concerning risk factors for delirium onset, this group's awareness of this information will unquestionably be of interest. The final report of the USH-chartered "Healthcare Workforce for Aging Veterans" Executive Taskforce has been the subject of three briefings with Dr. Petzel and, with his approval, is about to be presented to the National Leadership Board—it recommends focusing resources over the next 5 years on ensuring universal access within VHA to a single program in each of the inpatient, outpatient, and extended care areas—and for inpatient, that program is Geriatric Consultation, specifically targeting prevention, recognition, and management of inpatient delirium. Finally, the Deputy Under Secretary for Health for Operations and Management last month approved the formation of a Delirium Field Advisory Committee, charged with advising the GEC office on projects, programs, and activities that hold promise for enhancing awareness of and familiarity about delirium on the part of providers across the continuum of care.	
There is a potential for diagnosis of delirium with some of the tools reviewed. There is some low level evidence of preventive medications and possibly staff education that are useful in preventing delirium. The prevention of delirium could affect performance measures such as length of stay, length of ICU stay, decrease in morbidity, and decrease in NHPPD. This could have a positive impact on patient flow and improved discharge to home settings.	
The annual American Delirium Society conference and EES conferences during the last 3 years will be significantly impacted by these findings. In general, studies in the VA are nearly non-existent, yet VA eligible, VA using patients are sicker than any others in the country (Kazis data). In particular, younger veterans (Vietnam Era) have significant loads of comorbidity (often associated with PTSD as a contributing factor) and really need to be included in the "high risk" category although they don't meet usual age criteria. We may also see a need for OEF/OIF vets to be included for the same reason.	

REVIEWER COMMENT	RESPONSE
Inpatient nurses provide direct care to patients with delirium. The evidence in this report about non-pharmacological interventions to prevent delirium will be especially relevant to nurses in the acute care setting. Once the report is released, the Office of Nursing Services Evidence Based Practice Group will work with the Geriatric Nursing Field Advisory Committee to discuss how the information from this report on evidence-based nonpharmacological interventions can be disseminated to staff nurses and how we might enlist facilities to trial these evidence-based interventions.	
This report has the potential to impact the standard of care relative to screening of older Veterans for delirium at point of care.	
There is an ongoing quality improvement project in 5 – 7 ICUs measuring CAM ICU and RASS scores	
5. Please provide any recommendations on how this report can be revised to more directly address or assist implementation needs.	
Screening a. In the executive summary, it needs to explicitly state that studies are required in this area to improve detection b. The executive summary and document could use the information contained to highlight the incidence/prevalence of delirium. The goal is to make the statement that this is a common condition c. Targeting – who should the screening target (again using the EBR) o Older o Cognitively impaired o Sensory impairment d. Based on discussion/findings at a recent international meeting, it is fair to de-emphasize the CAM or at least include the requirement for additional mental status testing. e. On Page 14, there is a list of 'indirect links' – prevention needs to be added to this list	**Screening** a. The Future Research section indicates the need for a study of screening. b. We have added incidence/prevalence data to the background section of the executive summary and full report. c. The purpose of the evidence review is to present the evidence so that others make informed recommendations. d. Our report is based on published evidence. e. We have considered this suggestion but believe that prevention is not part of the indirect link. If a preventive strategy has been started, continued assessment of the patient would be considered monitoring of the success of the preventive strategy.
Prevention a. This review is incomplete by only 6-7 papers which were excluded based on a Cochrane review. These papers are described in the text, but not in the analysis and tables – Why not include them in this EBR to produce the most current EBR possible? o It is probably most important around the Marcantonio 2001 trial – which is extensively described b. The NICE guidelines (published 2 wks ago) are referenced. Did they include the methods (same issue different paper)? c. While this section focuses on prevention, the results of the rivastigmine in the ICU trial for delirium treatment (stopped due to increased mortality) might be important to cite/mention. d. Why was Kalisvaart's study not included in the meta analysis?\ e. There are at least two other studies in press on acetylcholinesterase inhibitors and delirium prevention (boustani and marcantonio) f. The limited evidence on general vs. regional anesthesia is surprising – consider reviewing Mason SE. J Alz Dis 2010;22;67-79 g. The risks and benefits of the non-pharmacological interventions should be mentioned (low risk interventions)	**Prevention** a. We have added the papers from the Cochrane Review and the NICE Guideline that met our study inclusion criteria. b. We have reviewed this document. c. We have reviewed the trial mentioned by the reviewer but have not included it in our review because rivastigmine was used for treatment, not for prevention. d. We have added the Kalisvaart study. e. As noted above, our inclusion criteria required articles be published in peer review manuscripts. f. We have reviewed this systematic review and have included 1 study that we had not already identified that met our inclusion criteria. g. Thank you for this suggestion. We have noted this in the report.

REVIEWER COMMENT	RESPONSE
Diagnosis a. The CAM requires supplemental mental status testing prior to completion. All validation studies of the CAM have completed the MMSE prior to completion. b. This needs to describe / inform about the education and training needed to complete these instruments and diagnose delirium. This is not 'off the shelf' stuff **Conclusions** a. De-emphasize CAM b. Highlight need for screening studies, limited evidence on pharm interventions, and education / training for diagnosis. Thus there is a strong need for additional studies and additional instruments for this disease	**Diagnosis** a., b.. These are important points and we have included this information in the findings for KQ3 and the conclusions. **Conclusions** a., b. Thank you for the suggestions. We have attempted to address them in the Conclusions and Future Research Needs sections.
The report points out the great amount of evidence in the field that is nonetheless non-definitive in its clinical application. The VA population (see above) really does require separate investigation. See Comments below.	We agree that the findings are generally of low-quality and/or insufficient.
Given the evidence presented, it is clear that much more research is needed to identify valid and reliable means of improving detection of delirium. A screening measure that can be universally implemented is needed. The CAM alone does not seem sufficient for this purpose – it requires supplemental mental status testing prior to completion. (Key Question #3) Recommendations for who to screen based on currently available evidence (older, sensory or cognitively impaired) should be highlighted. (Key Question #1)	We again emphasize that there are no data about the effectiveness and harms of screening for delirium in hospitalized medical patients. Therefore, we disagree that a screening measure that can be universally implemented is needed (or at least that such an instrument "should be implemented"). The current evidence does not permit making recommendations on who to screen.
More emphasis may also be placed on the non-pharmacological interventions for delirium prevention based in the evidence. These are low-cost, low-risk interventions.(Key Question #2)	We have added a table of risk ratios for the non-pharmacological interventions and more detail about the components of the multi-component interventions.
Limited evidence was reviewed regarding the need for education among providers that fail to recognize delirium across settings where Veterans receive care. (Key Question #1)	We have attempted to address this in the Key Question 1 conclusions.
Flip questions 1 and 3. In the summary, when a reader starts with "no convincing improvement in clinical outcomes, no convincing difference with different drugs, …. Many people won't get to 3. They want validation that their standard of care is fine. There is a way to measure brain dysfunction (which we call delirium like in the 18th century).	The questions are listed in the order originally agreed upon. No further change.
Additional Comments:	
I think this was a very thorough review of the literature and it was disheartening to see that there is little substantiated evidence on screening, identification and prevention of delirium. I did find 2 typos – page 18, first paragraph, states "following up" should state "follow up" Page 37 – typo of control group "if"29-60% and should be control group "of" 29-60%	Thank you for your comments. We have corrected the typos.
Investigations regarding deliriums that may be provoked ONLY by certain medication use (in the absence of other causes) would be very helpful; they may well have different prognoses than the multifactorial ones. This could help greatly because it would offer some "clean" recommendations that could easily be implemented very quickly through the VA.	Thank you for the suggestion. We have included this in the Future Research section.

REVIEWER COMMENT	RESPONSE
This is an important and complex topic for all staff who care for Veterans with delirium, in particular nursing staff who are with these Veterans 24/7 and understand the profound distress this condition causes for both Veterans and their family members. My comments are as follows:	
Introduction-page 4 Para 1: The 3 reasons that this review was undertaken are not listed in the order that the 3 key questions are discussed throughout this report (same inconsistency appears in the first paragraph of the Executive Summary)	We have corrected to ensure consistency.
Para 2: The authors state that they were "careful to make important distinctions between screening for delirium and diagnosis of delirium." This distinction is somewhat confusing in that the discussion of screening (para 1, page 13) suggests that the purpose of screening is to detect a condition before symptoms occur and the CAM is mentioned as a screen for delirium. Later, however, in the discussion of KQ3, CAM is discussed as a diagnostic tool (Key Question #3). Since the CAM items all address identifiable symptoms, is the CAM a screening test or a diagnostic tool or both? Are there any screening instruments for delirium that detect delirium in the preclinical state? Or are the delirium "screening instruments" really diagnostic instruments (tools)?	CAM could be used as both as a screening instrument in hospitalized patients (individuals without identifiable signs or symptoms of delirium) or as a diagnostic tool (patients with some signs or symptoms that are consistent with but not definitely determined to be delirium (e.g., a patient with confusion). KQ1 and the overarching goal of this report was to assess the effectiveness and harms as a screening tool including in individuals who may be at increased risk due to patient factors (e.g., age, personal history of delirium), index disease type or severity (e.g., stroke, ICU) or co-existing medical conditions/medications that are not directly the reason for admission (e.g. use of narcotics in a patient admitted for COPD). KQ3 assessed the use of CAM as both a diagnostic and screening tool as many of the studies evaluated patients with signs/ symptoms potentially compatible with delirium.
Background (page 4) In the 3rd sentence, paragraph 4, underlying causes of delirium are listed. The next sentence mentions "risk factors." Are underlying causes of delirium different from risk factors? Is so, what are the risk factors for delirium? Are orthopedic and cardiac surgeries risk factors for delirium or underlying causes of delirium? Most of the pharmacological studies discussed in KQ2 targeted patients who underwent either cardiac or orthopedic surgery yet surgery is not mentioned in para 4 on page 13 either as an underlying cause or risk factor for delirium.	We clarified our use of the term "risk factors". Causality is a strong term that definitely ascribes the outcome to the risk factor. We have clarified regarding surgery.
Key Question 1 (page 13) There is no discussion of who (MD, nurse, other staff?) would likely perform screening. In the screening studies/guidelines reviewed, was there mention of who completes the screening? This is an important question given that often the first contact a patient has in the inpatient setting is with a nurse.	This is a policy issue beyond the scope of the review. Screening if found to be effective could be implemented by several lines of health care staff including nurses and physicians and could be done at the admitting floor or in the clinic/emergency room where the admission decision was made. If screening for delirium is effective then future research should be conducted to assess the most effective/efficient methods for implementation.

REVIEWER COMMENT	RESPONSE
Key Question 2 Pharmacolgocial Studies Several different pharmacologic studies are discussed (pages 21-24 and 30-31). Most of the pharmacological studies with the exception of Dautezenberg et al (cholinesterase inhibitor) target patients who either underwent orthopedic or cardiac surgery. The report Conclusions on page 45 state, "Low level evidence suggests that pharmacologic strategies using analgesia via fascia iliaca compartmental block, antipsychotic, and lighter anesthesia may be useful in delirium prevention." • Since there are many causes of and many risk factors for delirium, would these pharmacological strategies be useful for "delirium prevention" as stated on page 45 or more specifically would they be useful for delirium prevention in patients undergoing surgical procedures? • The conclusion regarding pharmacological intervention on page 45 seems to imply that these pharmacological interventions would be useful in all patients with delirium when the studies targeted ortho and cardiac surgical patients.	We have clarified regarding surgery.
Non-pharmacological Studies On page 25 the report mentions that 9 multi-component studies consisted of interventions that significantly decrease the incidence of delirium. In the report Conclusions (page 45), multi-component interventions are again mentioned. It might be helpful for those staff interested in implementing multi-component interventions if examples were given of the intervention bundles trialed in some of these studies.	We have added information about the interventions in the multi-component studies.
Overall Organization While the discussion of each key question requires a somewhat different approach, there seems to be some inconsistencies in the overall organization of this report. 1. 1. Each of the key questions has multiple parts. a. On page 1, only the subparts of KQ 3 are designated as "a" and "b" b. While on page 2, the 4 subparts of KQ 2 are not designated as a-d, on pages 21-35, the subparts are designated as a-d. c. The 3 subparts of KQ1 are never designated as a-c. 2. KQ#1 ends with a "Conclusion"; KQ#2 ends with a "Summary of Finding"; and KQ3 ends abruptly with no conclusions or summary of findings.	We have corrected these inconsistencies.
Page 6/88 Key Question #1. Consider adding the positives… Lacking direct evidence, ¾ criteria establishing an indirect link between screening and outcomes for delirium were satisfied: 1) patents with delirium have worse outcomes, 2) systematic screening likely improves detection, and 3)harms associated with screening are likely minimal. However, we viewed evidence that treatments for delirium are effective is mixed. Page 17/88 Paragraph 1. Consider adding after Screening for disease or condition is warranted if the disease is serious ….. if treatment or therapeutic decisions would be altered in the presence of the condition.	We have modified this section. Without a systematic review of the evidence for each criterion, we are hesitant to say that the criteria were satisfied. Thank you – we have modified this statement.
This is an excellent, thorough review that emphasizes the need for research in delirium detection and prevention. I learned a lot by reading it.	Thank you.

APPENDIX D. EVIDENCE TABLES

Appendix D, Table 1: Characteristics of Pharmacologic Prevention Studies

Author, Year, Country, Study Design, Funding Source	Prevention Strategy Used, Controls	Inclusion and Exclusion Criteria, Recruitment Method	Patient Characteristics (expressed in means unless otherwise noted)	Outcomes Evaluated	Study Quality
Randomized trials					
Al-Aama, 2011[37] Canada Study Design: randomized controlled trial (RCT) Funding Source(s): Division of Geriatric Medicine, Department of Medicine, Schulich School of Medicine at The University of Western Ontario	Prevention Strategy Used: melatonin 0.5 mg orally prior to sleep (n=72) Controls: placebo (n=73)	Inclusion Criteria: at least 65 years of age and admitted through the emergency department to Internal Medicine in-patient services Exclusion Criteria: an expected stay or life expectancy of less than 48 hours, were unable to communicate in English or to take oral medications, had an intracranial bleed or seizures, had a markedly non-therapeutic international normalized ratio (INR) less than one or more than four while on warfarin, or had a known allergy to the study compounds Recruitment method: patients were approached directly in the emergency room or in their rooms by one of the three study clinicians within 24 hours of admission (up to 48 h was allowed on weekends)	N=145 Mean age (yrs): 84 Gender, male (%): 43 Race/ethnicity (%): NR Medical unit: Internal Medicine	Incidence of delirium (diagnosed within 6 days post-operatively with the Confusion Assessment Method (CAM)) Delirium severity (Memorial Delirium Assessment Scale) Use of sedatives Use of restraints	Allocation Concealment: adequate (pharmacy controlled) Blinding: double and outcomes assessment Intention to Treat Analysis (ITT): no, 23 patients excluded Withdrawals adequately described: yes
Larsen, 2010[38] US Study Design: RCT Funding Source(s): New England Baptist Hospital Research Department	Prevention Strategy Used: olanzapine 5 mg (oral) (n=243), administered perioperatively Controls: placebo (n=252)	Inclusion Criteria: history of postoperative delirium who were scheduled for elective total knee- or total hip-replacement surgery; ability to speak English; and ability to provide informed consent Exclusion Criteria: a diagnosis of dementia; active alcohol use; a history of alcohol dependence or abuse; allergy to olanzapine; and current use of an antipsychotic medication Recruitment method: NR	N=495 Mean age (yrs): 74 Gender, male (%): 46 Race/ethnicity (%): white 98, non white 2 Medical unit: orthopedic teaching hospital	Incidence of delirium (defined using the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition (DSM-III) Duration of delirium Delirium severity (Severity of delirium according to the highest value of the DRSR-98) Time-to-onset of delirium	Allocation Concealment: adequate (pharmacy controlled) Blinding: double and a independent data and safety monitoring committee evaluated all potentially serious adverse events Intention to Treat Analysis (ITT): no Withdrawals adequately described: yes

Author, Year, Country, Study Design, Funding Source	Prevention Strategy Used, Controls	Inclusion and Exclusion Criteria, Recruitment Method	Patient Characteristics (expressed in means unless otherwise noted)	Outcomes Evaluated	Study Quality
Sieber, 2010[39] US Study Design: RCT Funding Source(s): NA	Prevention Strategy Used: deep sedation with propofol (sedation depth using bispectral index (BIS) of approximately 50) (n=57) Controls: light sedation with propofol (BIS, ≥80) (n=57)	Inclusion Criteria: 65 years or older, undergoing hip fracture repair with spinal anesthesia and propofol sedation Exclusion Criteria: preoperative delirium (determined by CAM); contraindications to spinal anesthesia (e.g., clinically important aortic stenosis, coagulopathy, anticoagulant use, spinal cord disease, refusal of spinal anesthesia), prior hip surgery, severe congestive heart failure (New York Heart Association class IV), severe chronic obstructive pulmonary disease (Global Initiative for Chronic Obstructive Lung Disease guidelines, stage III-IV), or mental or language barriers that would preclude data collection Recruitment method: NR	N=114 Mean age (yrs): 82 Gender, male (%): 27 Race/ethnicity (%): NR Medical unit: multidisciplinary hip fracture service	Incidence of delirium (DSM-III) Delirium duration Time from surgery until discharge Mortality (during hospitalization)	Allocation Concealment: unclear Blinding: double Intention to Treat Analysis (ITT): yes Withdrawals adequately described: yes
Gamberini, 2009[40] Switzerland Study Design: RCT Funding Source(s): Novartis (partial support)	Prevention Strategy Used: rivastigmine (oral) 1.5 mg x 3/day (n=59), starting one day prior to surgery and then post-op for 6 days Controls: placebo (n=61)	Inclusion Criteria: age 65 or older and elective cardiac surgery with cardiopulmonary bypass Exclusion Criteria: urgent or emergency surgery, previous cardiac surgery, cardiac surgery combined with non-cardiac procedures (typically carotid endarterectomy), insufficient knowledge of German or sensory impairment interfering with neuropsychological testing, a preoperative Mini-Mental State Examination (MMSE) <15, psychiatric illness necessitating regular use of antidepressants or antipsychotics, preexisting neurologic deficits, previous or ongoing treatment with cholinesterase inhibitors, and known contraindications for rivastigmine Recruitment method: patients screened for eligibility based on the operation schedule for the following day	N=120, demographic information for 113 patients Mean age (yrs): 74 Gender, male (%): 68 Race/ethnicity (%): NR Medical unit: cardiac surgery	Incidence of delirium (diagnosed within 6 days post-operatively with the CAM) Rescue medication use	Allocation Concealment: adequate, (hospital pharmacy using identical bottles) Blinding: double Intention to Treat Analysis (ITT): no, 7 excluded from analyses Withdrawals adequately described: yes

Author, Year, Country, Study Design, Funding Source	Prevention Strategy Used, Controls	Inclusion and Exclusion Criteria, Recruitment Method	Patient Characteristics (expressed in means unless otherwise noted)	Outcomes Evaluated	Study Quality
Hudetz, 2009[41] US (Veterans) Study Design: RCT Funding Source(s): National Institutes of Health, United States Public Health Service, Medical College of Wisconsin Institutional Grant, departmental funds	Prevention Strategy Used: ketamine 0.5mg/kg intravenous bolus (n=29) Controls: placebo (n=29) ketamine or placebo administered during anesthetic induction in the presence of fentanyl and etomidate	Inclusion Criteria: at least 55 years of age, provided written informed consent before the initiation of any study-related procedures, scheduled for elective coronary artery bypass graft surgery or valve replacement/repair procedures with cardiopulmonary bypass; patients receiving antidepressants, stimulants, mood stabilizers, anxiolytics, or depressants were eligible Exclusion Criteria: history of cerebrovascular accident within 3 years of randomization, permanent ventricular pacing, previously defined cognitive deficits, patients receiving psychoactive drugs for the treatment of psychosis, hepatic impairment, chronic renal insufficiency, other pre-existing diseases deemed by the investigators to place the patient at an increased risk of perioperative complications Recruitment method: NR	N=58 Mean age (yrs): 64 Gender, male (%): 100 Race/ethnicity (%): white 90 Medical unit: cardiac surgery	Incidence of delirium (Intensive Care Delirium Screening Checklist) Length of stay	Allocation Concealment: unclear ("sealed envelopes") Blinding: double and outcomes assessment Intention to Treat Analysis (ITT): yes Withdrawals adequately described: no withdrawals
Maldonado, 2009[42] US Study Design: RCT Funding Source(s): none stated	Prevention Strategy Used: dexmedetomidine (loading dose: 0.4 µg/kg, followed by a maintenance drip of 0.2 µg/kg/hr–0.7 µg/kg/hr) (n=40) Controls: propofol: 25–50 µg/kg /min (n=38) midazolam: 0.5–2 mg/hr (n=40) All administered postoperatively	Inclusion Criteria: patients undergoing cardiac-valve operations with cardio-pulmonary bypass Exclusion Criteria: preexisting diagnosis of dementia or schizophrenia, the preoperative use of psychotropic medications, active or recent substance abuse or dependence, age less than 18 or older than 90 years, documented stroke within the last 6 months, evidence of advanced heart block, pregnancy, or anticipated intraoperative deep hypothermic circulatory arrest Recruitment method: NR	N=118 Mean age (yrs): 58 Gender, male (%): 64 Race/ethnicity (%): NR Medical unit: cardiac surgery	Incidence of delirium (DSM-IV) Length of stay (hospital and ICU) Rescue medication use (management of delirium) Mortality	Allocation Concealment: unclear Blinding: open-label Intention to Treat Analysis (ITT): no, 28 patients excluded (24%) Withdrawals adequately described: yes

Author, Year, Country, Study Design, Funding Source	Prevention Strategy Used, Controls	Inclusion and Exclusion Criteria, Recruitment Method	Patient Characteristics (expressed in means unless otherwise noted)	Outcomes Evaluated	Study Quality
Mouzopolous, 2009[43] Greece Study Design: RCT Funding Source(s): NR	Prevention Strategy Used: fascia iliaca compartment block (FICB) (n=102) - bupivicaine (0.3 mL/kg) 0.25 mg dose of on admission and repeated daily every 24 h until delirium occurrence or hip surgery was performed; 24 hours after hip surgery the same dose of FICB was re-administered and repeated daily every 24 h until delirium occurrence or discharge Controls: placebo (n=105)	Inclusion Criteria: Age 70 years and older admitted for hip fracture Exclusion Criteria: Delirium at admission, metastatic hip cancer, history of bupivicaine allergy, use of cholinesterase inhibitors, severe coagulopathy, Parkinsonism, epilepsy, levodopa treatment, delay of surgery of more than 72 h after admission, and inability to participate in interviews (profound dementia, respiratory isolation, intubation, aphasia, coma or terminal illness) Recruitment method: potentially eligible patients identified by systematically screening new admissions to one orthopedic ward	N=219, demographic information for 207patients Mean age (yrs): 73 Gender, male (%): 26 Race/ethnicity (%): NR Medical unit: orthopedics Risk classification based on 4 predictive risk factors: (1) severity of illness, measured using acute physiology age and chronic health examination; (2) cognitive impairment, measured using the mini-mental state examination score; (3) index of dehydration, measured using the ratio of blood urea nitrogen to creatinine; and (4) visual impair-ment, measured using the standardized Snellen test High risk defined as presence of three or more risk factors	Incidence of delirium (DSM-IV and CAM) Delirium severity (Severity of delirium according to the highest value of the DRSR-98) Delirium duration	Allocation Concealment: adequate, placebo identical in appearance to the active drug and was administered at the same site and in the same way as the FICB Blinding: patients blinded Intention to Treat Analysis (ITT): no, 12 excluded from analyses Withdrawals adequately described: yes

Author, Year, Country, Study Design, Funding Source	Prevention Strategy Used, Controls	Inclusion and Exclusion Criteria, Recruitment Method	Patient Characteristics (expressed in means unless otherwise noted)	Outcomes Evaluated	Study Quality
Prakanrattana, 2007[44] Thailand Study Design: RCT Funding Source(s): Non-industry (Siriraj Grant for Research Development)	Prevention Strategy Used: risperidone 1 mg (sublingual) when regaining consciousness post-op (n=63) Controls: placebo (n=63)	Inclusion Criteria: aged 40 years or older undergoing elective cardiac surgery with cardiopulmonary bypass Exclusion Criteria: patients undergoing emergency surgery, admitted to intensive care unit, tracheal intubation before arriving to operating room, patients experiencing preoperative delirium, history of psychiatric disorders Recruitment method: NR	N=126 Mean age (yrs): 61 Gender, male (%): 59 Race/ethnicity (%): NR Medical unit: cardiac surgery ICU	Incidence of delirium (CAM)	Allocation Concealment: possibly (no identical sublingual placebo but nurses taking care of the patient and assessing delirium left patient bedside to ensure blinding) Blinding: double Intention to Treat Analysis (ITT): yes Withdrawals adequately described: none reported
Sampson, 2007[45] UK Study Design: RCT Funding Source(s): Pfizer Esai, UK	Prevention Strategy Used: donepezil 5mg (n=21), following surgery and every day post-op x 3 days Controls: placebo (n=15)	Inclusion Criteria: patients undergoing elective total hip replacement Exclusion Criteria: patients with mini-mental state examination (MMSE) scores of < 26; patients with sensory impairment who could not undertake neuropsychological testing and those with known hypersensitivity to donepezil or piperidine derivatives or contraindications to the use of donepezil Recruitment method: all patients undergoing elective total hip replacement and attending the pre-admission assessment clinic, who were able to give informed consent, were invited to participate	N=50; demographic information for 33 patients Mean age (yrs): 68 Gender, male (%): 52 Race/ethnicity (%): NR Medical unit: orthopedics	Incidence of delirium (as indicated by the Delirium Symptom Interview) Length of hospital stay	Allocation Concealment: adequate, by the hospital pharmacy Blinding: double, and data were analyzed blind to randomization code Intention to Treat Analysis (ITT): no; 14 withdrawn after randomization; 3 excluded after treatment allocation Withdrawals adequately described: yes

Author, Year, Country, Study Design, Funding Source	Prevention Strategy Used, Controls	Inclusion and Exclusion Criteria, Recruitment Method	Patient Characteristics (expressed in means unless otherwise noted)	Outcomes Evaluated	Study Quality
Kalisvaart, 2005[46] The Netherlands Study Design: RCT Funding Source(s): NR	Prevention Strategy Used: haloperidol 1.5 mg/d (n=212), started preoperatively and continued for up to 3 days postoperatively Controls: placebo (n=218)	Inclusion Criteria: aged70 and older admitted for acute/ elective hip surgery and were at intermediate or high risk for postoperative delirium Exclusion Criteria: delirium at admission, no risk factors for postoperative delirium present at baseline, history of haloperidol allergy, use of cholinesterase inhibitors, parkinsonism, epilepsy, levodopa treatment, inability to participate in interviews, delay of surgery > 72 hours after admission, or a prolonged QTc interval of 460 ms or higher for men and 470 ms or higher for women on their electro-cardiogram Recruitment method: a research team of geriatricians and nurses in a single 915- bed teaching hospital identified potentially eligible patients by systematically screening new admissions to two surgical and three orthopedic wards	N=430 Mean age (yrs): 79 Gender, male (%): 20 Race/ethnicity (%): NR Medical unit: Surgical and orthopedic wards Risk classification based on presence of four predictive risk factors: (1) Visual impairment (binocular near vision worse than 20/70 after correction); (2) severity of illness, measured using the Acute Physiology Age and Chronic Health Examination (score of 16 or higher indicating increased severity); (3) cognitive impairment (MMSE score ≤ 24 on a scale of 0–30); and (4) index of dehydration (ratio of blood urea nitrogen to creatinine of ≥18) Intermediate risk -presence of 1or 2 risk factors High risk - presence of ≥ 3 risk factors	Incidence of post-operative delirium (DSM IV and Confusion Assessment Method criteria) Delirium duration Delirium severity (measured using the Delirium Rating Scale (DRS), revised version-98, range 0 (no severity) to 45 (high severity)). Length of stay	Allocation Concealment: adequate (hospital pharmacist had prepackaged) Blinding: double and members of the research team not involved in the clinical care of the patients performed all baseline and outcome assessments Intention to Treat Analysis (ITT): yes Withdrawals adequately described: yes

Author, Year, Country, Study Design, Funding Source	Prevention Strategy Used, Controls	Inclusion and Exclusion Criteria, Recruitment Method	Patient Characteristics (expressed in means unless otherwise noted)	Outcomes Evaluated	Study Quality
Liptzin, 2005[47] US Study Design: RCT Funding Source(s): Pfizer Corporation	Prevention Strategy Used: donepezil 14 days before and after surgery (n=39) Controls: placebo (n=41)	Inclusion Criteria: scheduled for elective total knee or hip arthroplasy and aged 50 or greater; able to give informed consent Exclusion Criteria: evidence of gastroesophageal reflux disease or sick-sinus syndrome; currently taking donepezil or previously intolerant of it; did not speak English; already in another trial Recruitment method: recruited from pts scheduled for elective total hip or knee arthroplasty	N=90 (Baseline info for 80; 58 completed trial) Mean age (yrs): 67 Gender, male (%): 43 Race/ethnicity (%): white 97.5, other 2.5 Medical unit: orthopedic surgery	Incidence of delirium (DSM-IV) Mean duration of post-op delirium Number with post-op subsyndromal delirium Mean duration of subsyndromal delirium Mean length of stay	Allocation Concealment: adequate (by pharmacist) Blinding: double Intention to Treat Analysis (ITT): no, 10 not operated on were excluded Withdrawals adequately described: yes
Papaioannou, 2005[48] Greece Study Design: RCT Funding Source(s): European Commission's BIOMED2 program BMH4-98-3335 and Greek Ministry of Health.	Prevention Strategy Used: regional anesthesia (epidural or spinal) (n=25) Controls: general anesthesia (n=25)	Inclusion Criteria: aged at least 60 years, scheduled for elective surgery that could be performed under regional or general anesthesia and who had agreed to be randomly allocated to receive either type of anesthesia Exclusion Criteria: illiteracy, severe auditory or visual disturbances, central nervous system disorders, alcoholism or drug dependence, treatment with tranquillizers or antidepressants, Parkinson's disease and a preoperative MMSE score ≤ 23 points, indicative of dementia Recruitment method: NR	N=50 (Baseline info for 47) Median age (yrs): 68 Gender, male (%): 64 Race/ethnicity (%): NR Medical unit: surgery (orthopedic and vascular)	Incidence of delirium (DSM-III)	Allocation Concealment: unclear Blinding: none stated Intention to Treat Analysis (ITT): no, 3 patients were excluded Withdrawals adequately described: yes
Aizawa, 2002[49] Japan Study Design: RCT Funding Source(s): none stated	Prevention Strategy Used: delirium free protocol, post surgery; diazepam 0.1 mg/kg IM at 20;00; flunitrazepam 0.04 mg/kg and pethidine 1 mg/kg continuous IV infusions for 8 hours x 3 nights (n=20) Controls: usual care (n=20)	Inclusion Criteria: patients aged over 70 but less than 86 years of age who underwent resection of gastric or colorectal cancer through an open laparotomy under general anesthesia Exclusion Criteria: liver cirrhosis or liver dysfunction, renal dysfunction, respiratory disturbance, other poor risk factors, mental disorders, visual impairment, or patients who required extensive resection of other organs or emergency surgery Recruitment method: NR	N=42 (Baseline info for 40; 2 excluded due to incomplete administration of agents) Mean age (yrs): 76 Gender, male (%): 65 Race/ethnicity (%): NR Medical unit: surgery	Incidence of delirium (DSM-IV) Mean length of stay	Allocation Concealment: unclear Blinding: outcomes assessor Intention to Treat Analysis (ITT): no, 2 were excluded Withdrawals adequately described: yes

Author, Year, Country, Study Design, Funding Source	Prevention Strategy Used, Controls	Inclusion and Exclusion Criteria, Recruitment Method	Patient Characteristics (expressed in means unless otherwise noted)	Outcomes Evaluated	Study Quality
Williams-Russo, 1992[13] US Study Design: RCT Funding Source(s): National Institute of Aging	Prevention Strategy Used: continuous epidural bupivicaine and fentanyl infusions (n=26). Initiated post-op at first complaint of pain Controls: continuous intravenous fentanyl infusions (n=25). Initiated post-op at first complaint of pain	Inclusion Criteria: scheduled for a bilateral knee replacement, speak English as a primary language, and have no serious hearing or vision impairment which would preclude cognitive testing Exclusion Criteria: none stated Recruitment method: bilateral knee surgery patients were approached	N=51 Mean age (yrs): 68 Gender, male (%): 45 Race/ethnicity (%): NR Medical unit: Urban referral hospital specializing in elective orthopedic surgery	Incidence of delirium (DSM-III)	Allocation Concealment: unclear Blinding: physicians and nurses administering care not aware of purpose of study; study personnel not involved in patient care/treatment decisions Intention to Treat Analysis (ITT): no Withdrawals adequately described: yes
Kaneko, 1999[50] Japan Study Design: RCT Funding Source(s): Not reported	Prevention Strategy Used: intravenous haloperidol (5 mg in 1.0mL daily) from 1st to 5th post-operative day (n=38) Controls: equal volume of normal saline injection (0.9%) (n=40)	Inclusion Criteria: patients scheduled for elective gastrointestinal surgery, admitted to High and Intensive Care Unit before scheduled surgery Exclusion Criteria: none stated Recruitment method: iInterviewed after admission	N=80 (2 patients excluded, unclear if excluded before or after randomization) Mean age (yrs): 72.8 Gender, male (%): 63 Race/ethnicity (%): NR Medical unit: high and Intensive Care Unit for gastrointestinal surgery	Incidence of delirium (DSM-III-R)	Allocation Concealment: unclear Blinding: none reported Intention to Treat Analysis (ITT): unclear Withdrawals adequately described: no – unclear when 2 patients were excluded

Author, Year, Country, Study Design, Funding Source	Prevention Strategy Used, Controls	Inclusion and Exclusion Criteria, Recruitment Method	Patient Characteristics (expressed in means unless otherwise noted)	Outcomes Evaluated	Study Quality
Berggren, 1987[51] Sweden Study Design: RCT Funding Source(s): Swedish Medical Research Council, No. 12x-5664, King Gustav V's 80th Birthday Foundation, and the Urnei University Research Foundation	Prevention Strategy Used: epidural anesthesia (n=28) Controls: halothane anesthesia (n=29)	Inclusion Criteria: patients admitted to the orthopedic wards for femoral neck fractures and were fully lucid Exclusion Criteria: none stated Recruitment method: NR	N=57 Mean age (yrs): 78 Gender, male (%): 19 Race/ethnicity (%): NR Medical unit: orthopedic wards	Incidence of delirium (DSM-III) Mean length of stay Mortality	Allocation Concealment: unclear Blinding: outcomes assessor Intention to Treat Analysis (ITT): yes Withdrawals adequately described: yes
Non-randomized trials					
Katznelson, 2009[52] Canada Study Design: prospective observational study Funding Source(s): University of Toronto	Prevention Strategy Used: statins (n=676) Controls: no statins (383)	Inclusion Criteria: patients undergoing cardiac surgery Exclusion Criteria: patients undergoing congenital or redo surgery, or requiring circulatory arrest, were excluded Recruitment method: NA	N=1059 Mean age (yrs): NA Gender, male (%): 71 Race/ethnicity (%): NR Medical unit: cardiovascular ICU	Incidence of delirium (diagnosed with CAM), presented as an odds ratio and also stratified by age groups (age <60 years and ≥ 60 years)	Allocation Concealment: Not applicable (NA) Blinding: single blinded (nursing staff) Intention to Treat Analysis (ITT): NA Withdrawals adequately described: NA

Author, Year, Country, Study Design, Funding Source	Prevention Strategy Used, Controls	Inclusion and Exclusion Criteria, Recruitment Method	Patient Characteristics (expressed in means unless otherwise noted)	Outcomes Evaluated	Study Quality
Del Rosario, 2008[53] Spain Study Design: retrospective comparison Funding Source(s): NR	Prevention Strategy Used: patient-controlled femoral nerve analgesia (n=49) Controls: intravenous analgesia (n=50)	Inclusion Criteria: ≥ 50 years old; underwent hip fracture surgery with intradural anesthesia Exclusion Criteria: received general· anesthesia or epidural analgesia, presented failure of femoral analgesia, or had localized infection or coagulopathy Recruitment method: NA, chart review	N=99 Mean age (yrs): 81 Gender, male (%): Intervention: 20, Control: 38, p=0.08 Race/ethnicity (%): NR Medical unit: orthopedics	Incidence of delirium (documentation of altered mental status (confusion, disorientation, changes of level of consciousness, changes in the sleep-wake cycle)) Delirium severity (classified into two degrees of severity, low or severe, according to the need of prescription of any antipsychotic drug) Rescue medication use	Allocation Concealment: NA Blinding: NA Intention to Treat Analysis (ITT): NA Withdrawals adequately described: NA
Dautzenberg, 2004[12] The Netherlands Study Design: Retrospective cohort study Funding Source(s): NR	Prevention Strategy Used: rivastigmine chronic users (n=11) Controls: non-rivastigmine users (n=29)	Inclusion Criteria: patients who were treated by the geriatric consultation team and had the appearance of a delirium or were considered to be at high-risk of develop delirium by their treating physician Exclusion Criteria: NR Recruitment method: group of 366 hospitalized patients, treated by the geriatric consultation team from January 2002 to June 2003, chronic rivastigmine users compared with randomly selected subgroup of all patients not treated with rivastigmine.	N=40 Mean age (yrs): 79 Gender, male (%): 40 Race/ethnicity (%): NR Medical unit: Non-geriatric wards	Diagnosed delirium during the time of hospitalization of the patient (based on DSM-IV criteria, and recorded in the medical record) Length of hospital stay Mortality	Allocation Concealment: NA Blinding: NA Intention to Treat Analysis (ITT): NA Withdrawals adequately described: NA
Savage, 1978[54] US Study Design: non-random comparison Funding Source(s): NR	Prevention Strategy Used: physostigmine (n=45) Controls: No physostigmine (n=68)	Inclusion Criteria: randomly selected pts who underwent elective surgery and were either Status I or II (American Society of Anesthesiologists) Exclusion Criteria: bradycardia, bronchial asthma, obstructive pulmonary disease, pregnancy, Parkinson's Recruitment method: NA	N=113 Mean age (yrs): NR Gender, male (%): NR Race/ethnicity (%): NR Medical unit: surgical	Subjects were evaluated, post-surgery, on the following scale: 1) restless, thrashing, a score of 1; 2) mumbling, incoherent, a score of 2; 3) reacting, quiet, but nonverbal, a score of 3; 4) and appropriate verbal responses, a score of 4	Allocation Concealment: NA Blinding: nurses who graded delirium, were blinded to intervention Intention to Treat Analysis (ITT): NA Withdrawals adequately described: NA

Appendix D, Table 2. Primary Prevention Outcomes of Pharmacologic Studies

Author, Year *Drug class*	Delirium Incidence/ Prevalence n/N (%)		Delirium Severity (SD unless noted)		Delirium Duration, days (SD unless noted)		Length of Stay, days (SD unless noted)		Use of Rescue Medications n/N (%)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Randomized studies										
Al-Aama 2011[37] *Melatonin*	7/61 (11.5) p=0.01	19/61 (31.1)	MDAS delirium only 10.5 (5.3) p=0.77	 delirium only 11.4 (3.0)			18.5 (26.4) p=0.36	14.5 (21.6)	PRN sedatives 33/61 (54.1) p=0.46	PRN sedatives
Larsen 2010[38] *Antipsychotic*	28/196 (14.3) p<0.0001	82/204 (40.2)	DRSR-98 16.4 (3.7) p=0.02	DRSR-98 14.5 (2.7)	2.2 (1.3) p=0.02	1.6 (0.7)			A trend toward use of fewer narcotics in the intervention arm but difference not significant	
Sieber 2010[39] *Anesthesia*	Light sed. 11/57 (19) p=0.02	Deep sed. 23/57 (40)	MMSE score 2 days post-op 23.1 (5.5) p=0.08 Change from baseline -2.1 (3.4) p=0.06	MMSE score 2 days post-op 20.0 (9.3) Change from baseline -4.4 (6.1)	Light sed. All 0.5 (1.5) delirium only 2.8 (2.3) p=0.77	Deep sed. All 1.4 (4.0) p=0.01 delirium only 3.4 (5.7)	Light sed. mean 4.7 (3.1) p=0.69	Deep sed. Mean 4.5 (2.3)		
Gamberini 2009[40] *Cholinesterase inhibitor*	18/56* (32.1) **p=0.79	17/57* (29.8)			Median 2.5 (range 1-5) p=0.30	Median 3 (range 1-5)	Median 13 (range 7-39) p=0.3	Median 13 (range 7-39)	Haloperidol 17/56 (30.4) p=0.90 Lorazepam 35/56 (62.5) p=0.70	Haloperidol 18/57 (30.4) Lorazepam 38/57 (66.7)
Hudetz 2009[41] *Anesthesia*	1/29 (3.4) p=0.01	9/29 (31.0)					8 (4.0) p=0.36	7 (3.0)		
Maldonado 2009[42] *Postoperative sedation*	Dexmedet. 4/40 (10.0) p<0.001 both controls *Per protocol* Dexmedet. 1/30 (3.3) p<0.001 both controls	Propofol 16/36 (44.4) Midazolam 17/40 (42.5) *Per protocol* Propofol 15/30 (50.0) Midazolam 15/30 (50.0)			Dexmedet. 2.0 (0.0) p=0.93 vs. propofol, 0.63 vs. midazolam	Propofol 3.0 (3.1) Midazolam 5.4 (6.6)	Dexmedet. 7.1 (1.9) p=0.42 vs. propofol, 0.12 vs. midazolam	Propofol 8.2 (3.8) Midazolam 8.9 (4.7)	Haloperidol Dexmedet. 0/30 p=0.07 vs. propofol, 0.15 vs. midazolam Lorazepam Dexmedet. 1/30 (3.3) p=0.06 vs. propofol, 0.11 vs. midazolam	Haloperidol Propofol 3/30 (10.0) Midazolam 2/30 (6.7) Lorazepam Propofol 7/30 (23.3) Midazolam 6/30 (20.0)

Author, Year *Drug class*	Delirium Incidence/ Prevalence n/N (%)		Delirium Severity (SD unless noted)		Delirium Duration, days (SD unless noted)		Length of Stay, days (SD unless noted)		Use of Rescue Medications n/N (%)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Mouzopolous 2009[43] *Analgesia*	All* 11/102 (10.8) p=0.017 High risk group 9/17 (52.9) p=0.73	All* 25/105 (23.8) High risk group 10/16 (62.5)	DRSR-98 Highest value 14.3 (3.6) p<0.001	DRSR-98 Highest value 18.6 (3.4)	5.2 (4.3) p<0.001	11 (7.2)				
Prakanrattana 2007[44] *Antipsychotic*	7/63 (11.1) p=0.01	20/63 (31.7)								
Sampson 2007[45] *Cholinesterase inhibitor*	2/19 (10.5) p=0.08	5/14 (35.7)					9.9 (0.7) p=0.09	12.1 (1.1)		
Kalisvaart, 2005[46] *Antipsychotic*	32/212 (15.1) p=0.69	36/218 (16.5)	Based on DRS, range 0-45 14.4 (3.4) p<0.001	Based on DRS, range 0-45 18.4 (4.3)	5.4 (4.9) p<0.001	11.8 (7.5)	All 13.8 (7.7) p=0.84 Delirious pts. only 17.1 (11.1) p<0.001	All 13.6 (7.8) Delirious pts. only 22.6 (16.7)		
Liptzin 2005[47] *Cholinesterase inhibitor*	DSM-IV 8/39 (20.5) p=0.69 Subsyndromal (Sub) 28/39 (71.8) p=0.57	DSM-IV 7/41 (17.1) Sub. 27/41 (65.8)			DSM-IV 1.0 (SE 0.0) p=0.12 Sub. 1.71 (SE 0.19)	DSM-IV 1.3 (SE 0.19) Sub. 2.04 (SE 0.23)	4.4 (SE 0.13)	4.2 (SE 0.08)		
Papaioannou 2005[48] *Anesthesia*	Regional 3/19†† (15.8) p=0.63	General 6/28†† (21.4)								
Aizawa 2002[49] *Delirium free protocol (DFP) (Benzodiaze-pines)*	DFP 1/20 (5.0) p=0.06 Accidents cause by delirium‡ 1/20 (5.0) p=0.10	Control 7/20 (35.0) Accidents cause by delirium‡ 5/20 (25.0)					DFP 25.6 (9.4) p=0.74	Control 29.9 (16.2)		

Author, Year *Drug class*	Delirium Incidence/ Prevalence n/N (%)		Delirium Severity (SD unless noted)		Delirium Duration, days (SD unless noted)		Length of Stay, days (SD unless noted)		Use of Rescue Medications n/N (%)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Williams-Russo 1992[13] *Analgesia*	Bupivivicaine +Fentanyl 10/26 (38.4) p=0.69	Fentanyl 11/25 (44.0)								
Kaneko, 1999[50] *Antipsychotic*	4/38 (10.5) p<0.05	13/40 (32.5)								
Berggren 1987[51] *Anesthesia*	Epidural 14/28 (50.0) p=0.36	Halothane 11/29 (37.9)								
Non-randomized studies										
Katznelson, 2009[52] *Antilipid therapy*	All 73/676 (10.8) p=0.33 Age < 60 9/188 (4.8) Age 60+ 64/488(13.1)	All 49/383 (12.8) Age < 60 12/197(6.1) Age 60+ 37/186(19.9)								
Del Rosario 2008[53] *Analgesia*	4/49 (8.2) p<0.001 Severe 0/49	21/50 (42.0) Severe 11/50 (22)					7.7 (3.0) p=0.16	8.6 (3.5)	Opioids 0/49 p<0.001	Opioids 14/50 (28)
Dautzenberg 2004[12] *Cholinesterase inhibitor*	5/11 (45.5) p=0.01	26/29 (88.9)					40.6 (95%CI -20-101.2); p=0.73	28.4 (95%CI (-16.8-73.6)		
Savage 1978[54] *Cholinesterase inhibitor*	Score of 1 or 2† 4/45 (8.9); p<0.01 Score of 1, 2 or 3† 13/45 (28.9); p<0.001	Score of 1 or 2† 29/68 (42.6) Score of 1, 2 or 3† 47/68 (69.1)								

*Number analyzed or completed trial

** All p-values are versus control. If not provided, they were calculated by the reviewers.

† 1 = a restless, thrashing patient, who is a danger to himself and required physical restraint; 2 = a mumbling, groaning, incoherent, unresponsive patient; 3 = a reacting, quiet, non-verbal patient who responded to all verbal commands; 4 = an awake patent who appropriate verbal responses.

†† Data were analyzed per protocol. 25 patients each were randomized to the regional and general anesthesia arms, respectively. 4 patients receiving regional anesthesia failed and crossed over to general and 3 patients (2 regional, 1 general) refused to go with study and were then excluded. Final n=47 (19 regional and 28 general).

‡ 5 patients pulled out nasal-gastric tube, one pulled out central vein line, and all showed “strange behavior” like peeling off dressing gauze or fumbling with tubes.

Appendix D, Table 3: Characteristics of Non-Pharmacologic or Mixed Treatments Prevention Studies

Author, Year, Country, Study Design, Funding Source	Prevention Strategy Used, Controls	Inclusion and Exclusion Criteria, Recruitment Method	Patient Characteristics (expressed in means unless otherwise noted)	Outcomes Evaluated	Study Quality
Randomized Trials					
Lundstrom, 2007[55] Sweden Study Design: RCT Funding Source(s): non-industry (Vardal Fdn, Joint Committee of the Northern Health Region of Sweden, JC Kempe Memorial Fdn, Fdn of the Medical Faculty, Univ of Umea, County Council of Vasterbotten, Swedish Research Council)	Prevention Strategy Used: post operative multi-factorial intervention program (n=102); intervention consisted of staff education focusing on the assessment, prevention and treatment of delirium and associated complications Controls: postoperative care in the Orthopedic Department according to the usual postoperative care routines (n=97)	Inclusion Criteria: aged 70 years or older, consecutively admitted to the Orthopedic Department at the University Hospital in Umea, Sweden, between May 2000 and December 2002 with femoral neck fracture Exclusion Criteria: severe rheumatoid arthritis, severe hip osteoarthritis, severe renal failure, pathological fracture, bedridden status prior to fracture Recruitment Method: in emergency room, patients were asked both in writing and orally if they were willing to participate in the study; in the case of patients with cognitive impairment, next-of-kin were also asked	N=199 Mean age (yrs): 82 Gender, male (%): 26 Race/ethnicity (%): NR Medical unit: specialized geriatric ward or conventional orthopedic ward	Delirium prevalence (defined as DSM IV) Delirium duration Length of stay Mortality	Allocation Concealment: yes (sealed and opaque envelopes) Blinding: outcomes assessor Intention to Treat Analysis (ITT): yes Withdrawals adequately described: yes
Taguchi, 2007[56] Japan Study Design: RCT Funding Source(s): NR	Prevention Strategy Used: bright light therapy (n=8) Controls: natural lighting environment (n=7)	Inclusion Criteria: middle-aged or aged patients who had no mental or ophthalmologic disorders and were capable of communication in Japanese Exclusion Criteria: NR Recruitment Method: Patients undergoing surgery for esophageal cancer were recruited	N=15 Mean age (yrs): 58 Gender, male (%): 100 Race/ethnicity (%): NR Medical unit: ICU	Delirium incidence (defined using Japanese version (2001) of the NEECHAM Confusion Scale)	Allocation Concealment: unclear Blinding: NR Intention to Treat Analysis (ITT): no, 4 excluded from analyses Withdrawals adequately described: yes (reintubated patients and patients with complications excluded)

Author, Year, Country, Study Design, Funding Source	Prevention Strategy Used, Controls	Inclusion and Exclusion Criteria, Recruitment Method	Patient Characteristics (expressed in means unless otherwise noted)	Outcomes Evaluated	Study Quality
McCaffrey, 2006[57] United States Study Design: RCT Funding Source(s): NR	Prevention Strategy Used: usual post-operative care plus music (patient's choice from CDs provided) played at least 1 hour, 4 times/day (n=62) Controls: usual post-operative care (no music protocol) (n=62)	Inclusion Criteria: elders undergoing elective hip or knee surgery; over 65 years of age; alert and oriented to provide consent to surgery and to complete preoperative paperwork independently; able to hear music Exclusion Criteria: NA Recruitment Method: recruited during pre-op interview	N=126 (124 completed the study) Mean age (yrs): 77 Gender, male (%): 36 Race/ethnicity (%): NR Medical unit: large tertiary care center (orthopedic)	Delirium incidence (based on review of nurses' notes after patient was discharged)	Allocation Concealment: unclear Blinding: none Intention to Treat Analysis (ITT): no Withdrawals adequately described: yes
Lundstrom, 2005[58] Sweden Study Design: RCT Funding Source(s): Non-industry (Joint Committee of the Northern Health Region of Sweden and others)	Prevention Strategy Used: intervention ward (n=200); multi-component including education in geriatric medicine focusing on assessment, prevention, and treatment of delirium, education concerning caregiver-patient interaction focusing on patients with dementia and delirium, reorganization from a task-allocation care system to a patient-allocation system with individualized care, monthly guidance for nursing staff Controls: control ward care (usual hospital care) (n=200)	Inclusion Criteria: aged 70 and older Exclusion Criteria: patient refusal Recruitment Method: patients mainly (93.8%) admitted from the emergency room in the same proportion to each ward	N=400 Mean age (yrs): 80.1 Gender, male (%): 44 Race/ethnicity (%): NR Medical unit: general internal medicine	Delirium incidence, (defined by DSM-IV) Delirium duration	Allocation Concealment: unclear Blinding: outcomes assessor Intention to Treat Analysis (ITT): yes Withdrawals adequately described: all included
Marcantonio, 2001[59] United States Study Design: RCT Funding Source(s): Older Americans Independence Center; Charles Farnsworth Trust	Prevention Strategy Used: proactive geriatrics consultation, preoperatively or within 24 hours of surgery (n=62) Controls: Usual care (n=64)	Inclusion Criteria: patients 65 years or older admitted for primary surgical repair of hip fracture Exclusion Criteria: presence of metastatic cancer or other comorbid illness likely to reduce life expectancy to less than 6 months, or inability to give informed consent with 24 hours of surgery or 48 hours from admission Recruitment Method: patients approached by investigators after admitted	N=126 Mean age (yrs): 79 Gender, male (%): 21 Race/ethnicity (%): white 90 Medical unit: orthopedic surgery	Delirium incidence (CAM) Severe delirium incidence (CAM-defined delirium with MDAS score ≥18) Delirium duration Length of stay	Allocation Concealment: unclear ("sealed envelopes") Blinding: outcomes assessor for delirium incidence Intention to Treat Analysis (ITT): yes Withdrawals adequately described: all included

Author, Year, Country, Study Design, Funding Source	Prevention Strategy Used, Controls	Inclusion and Exclusion Criteria, Recruitment Method	Patient Characteristics (expressed in means unless otherwise noted)	Outcomes Evaluated	Study Quality
Non-randomized studies					
Ushida, 2009[60] Japan Study Design: Prospective cohort with retrospective control Funding Source(s): None	Prevention Strategy Used: postoperative care under modified protocols were prospectively examined (n=41) Controls: cervical myelopathy patients were retrospectively examined about the incidence of post- operative delirium (n=81)	Inclusion Criteria: patients who met indication criteria for cervical decompression surgery Exclusion Criteria: dementia, other psychological disorders Recruitment Method: NA	N=122 Mean age (yrs): Intervention: 68 Control: 70 Gender, male (%): NR Race/ethnicity (%): NR Medical unit: neurology (spinal surgery)	Delirium incidence (based on DSM-IV criteria)	Allocation Concealment: NA Blinding: NA Intention to Treat Analysis (ITT): NA Withdrawals adequately described: NA
Vidan, 2009[61] Spain Study Design: controlled clinical trial Funding Source(s): Non-industry (Spanish Geriatrics Society)	Prevention Strategy Used: quality improvement program with two major components: an educational program aimed at changing the approach of geriatric ward staff to patient care and a set of specific targeted actions in 7 risk factor domains (orientation, sensorial perception, sleep preservation, mobilization, hydration, nutrition, drug list review) (n=172) Controls: standard care provided by internists, nurses, and additional staff (nutritionists, rehabilitation team, social workers), when needed (n=372)	Inclusion Criteria: aged 70 and older, with any of the risk criteria for delirium (cognitive impairment, visual impairment, acute disease severity, dehydration) Exclusion Criteria: presence of severe dementia that impaired communication, aphasia of any origin, coma, agonic status, or expected hospital stay less than 48 hours Recruitment Method: patients who did not have delirium at the time of admission and had ≥ 1 of the four risk factors of delirium (cognitive impairment, visual impairment, acute disease severity, and dehydration) were included	N=542 Mean age (yrs): Intervention: 86 Control: 82 p<0.001 Gender, male (%): Intervention: 38 Control: 47 p=0.04 Race/ethnicity (%): NR Medical unit: Internal medicine or geriatrics *Note: there were significant differences (p<0.05)in several of the baseline characteristics*	Delirium incidence (defined according to the criteria of the CAM) Delirium severity (measured using an additive score for the four delirium symptoms included in the CAM; evaluator rated each delirium symptom, except fluctuation, as absent (0 points), mild (1 point), or severe (2 points); fluctuation was rated as absent (0 points) or present (1 point); sum of these points ranged from 0 to 7 with higher scores indicating greater severity) Delirium duration Mortality	Allocation Concealment: NA Blinding: A trained research assistant, who was not involved in the intervention, conducted all interviews. Intention to Treat Analysis (ITT): yes Withdrawals adequately described: NA

Author, Year, Country, Study Design, Funding Source	Prevention Strategy Used, Controls	Inclusion and Exclusion Criteria, Recruitment Method	Patient Characteristics (expressed in means unless otherwise noted)	Outcomes Evaluated	Study Quality
Kratz, 2008[62] United States Study Design: quasi-experimental Funding Source(s): none stated	Prevention Strategy Used: acute confusion (AC) protocol, an evidence-based project which focused on 3 protocols (1) patient orientation (2) non-pharmacologic sleep; and (3) early mobilization; implemented by an interdisciplinary team (pharmacists, occupational therapists, physical therapists, nurses, and nurses' aides) Pilot study: two units each chose an intervention to implement for 1 month Following pilot study, implementation of all 3 protocols was initiated Controls: pilot study: one unit continued usual care of the elderly	Inclusion Criteria: 70 years or older, admitted for more than 23 hours, and without a communication barrier or having an alcohol withdrawal experience Exclusion Criteria: none stated Recruitment Method: NA	N=137 (pilot study) Mean age (yrs): NR, all >70 years of age Gender, male (%): NR Race/ethnicity (%): NR Medical unit: medical/surgical	Delirium (AC) incidence in the pilot study Rate of falls Use of restraints Usage of anti-anxiety medications (known to cause acute confusion)	Allocation Concealment: NA Blinding: NA Intention to Treat Analysis (ITT): NA Withdrawals adequately described: NA
Robinson, 2008[63] Vollmer, 2007[64] United States Study Design: pre- and post-intervention study; data collected using retrospective record review Funding Source(s): none stated	Prevention Strategy Used: delirium protocol - interventions from the HELP program and strategies suggested by Foreman et al. (2003)* - implemented in a post-intervention group; interventions implemented by nursing assistants and included specific approaches for patients with dementia, hearing impairment, vision impairment, and mobility impairment (n=80) Controls: matched convenience sample of patients over the age of 65 with any combination of the risk factors of the post-intervention group who were admitted prior to the implementation of the delirium prevention protocol (n=80) *Foreman MD, Mion LC, Trygstad LJ, Fletcher K. (2003). Delirium: Strategies for assessing and treating. In M. Mezey, et al. (Eds.). Geriatric nursing protocols for best practice (2nd ed., pp. 63–75). New York: Springer.	Inclusion Criteria: over the age of 65 with any combination of the risk factors of dementia, vision impairment, hearing impairment, and mobility impairment Exclusion Criteria: NR Recruitment Method: on admission, patients over 65 were assessed for risk factors of dementia, vision impairment, hearing impairment, and mobility impairment by the registered nurse admitting the patient	N=160 Mean age (yrs): Pre-intervention (control) group: 79.2 Post-intervention group: 78.8 Gender, male (%):46% Race/ethnicity (%): NR Medical unit: renal	Delirium incidence (defined according to the criteria of the CAM)	Allocation Concealment: NA Blinding: NA Intention to Treat Analysis (ITT): NA Withdrawals adequately described: NA

Author, Year, Country, Study Design, Funding Source	Prevention Strategy Used, Controls	Inclusion and Exclusion Criteria, Recruitment Method	Patient Characteristics (expressed in means unless otherwise noted)	Outcomes Evaluated	Study Quality
Caplan, 2007[65] Australia Study Design: controlled before-and-after study Funding Source(s): Non-industry (Commonwealth Department of Health and Aging)	Prevention Strategy Used: volunteer-mediated intervention of daily orientation, therapeutic activities, feeding and hydration assistance, vision and hearing protocols based on the Hospital Elder Life Program (HELP) developed at Yale University School of Medicine; training materials purchased through the HELP mentorship program and adapted to POWH so that the whole intervention could be delivered by volunteers; volunteer coordinator employed to select, train and oversee volunteers delivering a set of interventions to elderly patients (n=16) Controls: usual care (n=21)	Inclusion Criteria: at least one of the following risk factors for developing delirium: mini-mental state examination < 24, sleep deprivation, any activities of daily living, impairment or immobility, vision impairment, hearing impairment or dehydration Exclusion Criteria: severe dementia (MMSE < 10), psychotic disorder; unable to consent or refused; terminal condition receiving comfort care; to be discharged within 48; any behavioral or medical condition that may place the volunteer's health and safety at risk Recruitment Method: patients able to communicate and aged greater than 70 years were enrolled on admission to the geriatric wards	N=37 Mean age (yrs): Intervention: 84 Control: 86 p=0.4 Gender, male (%): 22 Race/ethnicity (%): NR Medical unit: Geriatrics	Delirium incidence (CAM) Delirium severity (assessed using Memorial Delirium Assessment Score (MDAS)) Length of stay Cost analysis data provided	Allocation Concealment: NA Blinding: NR Intention to Treat Analysis (ITT): yes Withdrawals adequately described: none
Harari, 2007[66] United Kingdom Study Design: Prospective before-and-after study Funding Source(s): Guys and St. Thomas' Charity	Prevention Strategy Used: proactive care of older people undergoing surgery (POPS) – a multidisciplinary preoperative comprehensive geriatric assessment (CGA) and post-operative follow-up (n=54) Controls: pre-POPS (n=54)	Inclusion Criteria: elective orthopedic patients, age 65 and older Exclusion Criteria: none stated Recruitment Method: POPS targeted patients with risk factors for post-surgery complications; sought referrals for older patients needing surgery but considered too 'medically unfit"	N=108 Mean age (yrs): 74.6 Gender, male (%): 39.8 Race/ethnicity (%): NR Medical unit: elective orthopedic surgery	Delirium incidence (defined as acute change in mental status post-op with improvement pre-discharge) Length of stay Mortality (within 30 days)	Allocation Concealment: NA Blinding: outcomes assessment was non-blinded Intention to Treat Analysis (ITT): NA Withdrawals adequately described: all included

Author, Year, Country, Study Design, Funding Source	Prevention Strategy Used, Controls	Inclusion and Exclusion Criteria, Recruitment Method	Patient Characteristics (expressed in means unless otherwise noted)	Outcomes Evaluated	Study Quality
Naughton, 2005[67] United States Study Design: Cohort Funding Source(s): Non-industry (Kalieda Fdn & West NY AD Assistance Ctr)	Prevention Strategy Used: multifactorial: emergency physicians educated and reminded to evaluate patients >75 years old for dementia & delirium and to admit patients with dementia or delirium to the Acute Geriatric Unit (AGU); AGU protocol including nurse, physician and environmental interventions; nurse and physician education and feedback on performances (4-Month Outcome (n=154) and 9-Month Outcome (n=110)) Controls: pretest/ baseline patients admitted 9/98-11/98 to general med service (n=110)	Inclusion Criteria: ≥75 years, admitted to non-critical-care medical service of Buffalo General Hospital 4 months and 9 months after multi-factorial prevention program started Exclusion Criteria: admitted from nursing home, declined to be interviewed Recruitment Method: consecutive admissions to medical service	N=cohort of 110 patients evaluated at baseline (before prevention strategy implemented); cohort of154 patients evaluated 4 months after implementation; cohort of 110 patients evaluated 9 months after implementation; (total N=374) Mean age (yrs): baseline cohort: 81±6.2; 4-month cohort: 81±6.1; 9-month cohort: 82±5.9 Gender, male (%): baseline cohort: 41 (37%); 4-month cohort: 52 (34%); 9-month cohort: 38 (35%) Race/ethnicity (%): NR Medical unit: baseline cohort: general medicine; 4-month cohort: Acute Geriatric Unit (AGU; N=84) & general medicine (N=70); 9-month cohort: AGU (N=37) & general medicine (N=73)	Delirium prevalence (defined as +CAM) Medication use (benzodiazepines, antidepressants, antihistamines, opiates, neuroleptics)	Allocation Concealment: NA Blinding: NA Intention to Treat Analysis (ITT): NA Withdrawals adequately described: NA

Author, Year, Country, Study Design, Funding Source	Prevention Strategy Used, Controls	Inclusion and Exclusion Criteria, Recruitment Method	Patient Characteristics (expressed in means unless otherwise noted)	Outcomes Evaluated	Study Quality
Tabet, 2005[68] UK Study Design: single-blind case–control study Funding Source(s): NR	Prevention Strategy Used: intervention ward - educational package s delivered to medical and nursing staff; 3 components: (1) 1 hour session including a formal presentation and small group discussion; (2) written information and guidelines on how to prevent, recognize and manage delirium in older people; (3) regular one-to-one and small group discussions lasting up to an hour during which staff were encouraged to discuss discharged challenging cases they had encountered with the aim of enhancing their learning experience with specific examples (n=122) Controls: control ward -no educational package and established practice was maintained throughout (n=128)	Inclusion Criteria: 70 years of age or older, understood and spoke English, agreed to take part, had no recorded symptoms of delirium in medical and nursing notes on admission, and had been in hospital for longer than 24 hours Exclusion Criteria: NR Recruitment Method: all admissions to the two medical units between December 2001 and August 2002 were considered eligible for inclusion if they met the above criteria	N=250 Mean age (yrs): Intervention: 81 Control: 79 p=0.007 Gender, male (%): 48 Race/ethnicity (%): NR Medical unit: medicine	Point prevalence of delirium (defined using a modified Delirium Rating Scale (DRS))	Allocation Concealment: NA Blinding: single (patients) Intention to Treat Analysis (ITT): yes, however case notes of 6 patients on the intervention ward and 8 on the control ward could not be traced by the Medical Records Department and therefore were not examined Withdrawals adequately described: none reported
Wong Tim Niam, 2005[69] Australia Study Design: Before and after study Funding Source(s): NR	Prevention Strategy Used: program group - quality improvement methods including staff education and use of a checklist to facilitate use of the 10 strategies, including (1) maintenance of adequate brain oxygen delivery; (2) maintenance of fluid and electrolyte balance; (3) pain protocol; (4) active policy of discontinuing or minimizing medications; (5) regulation of bladder/ bowel function (6) adequate nutrition; (7) early mobilization and rehabilitation; (8) prevention, early detection and treatment of major peri- and post-operative complications; (9) appropriate environmental stimuli; (10) treatment protocol of agitated delirium (n=71) Control: no program group (n=28)	Inclusion Criteria: all patients with osteoporotic hip fracture aged over 50 years admitted during the study period Exclusion Criteria: < 50 years of age Recruitment Method: consecutive patients with hip fracture admitted to the orthopedic unit at Fremantle Hospital	N=99 Mean age (yrs): 82 Gender, male (%): 28 Race/ethnicity (%): NR Medical unit: orthopedic	Delirium incidence (assessed using CAM) Delirium duration Length of hospital stay	Allocation Concealment: NA Blinding: none Intention to Treat Analysis (ITT): yes Withdrawals adequately described: NA

Author, Year, Country, Study Design, Funding Source	Prevention Strategy Used, Controls	Inclusion and Exclusion Criteria, Recruitment Method	Patient Characteristics (expressed in means unless otherwise noted)	Outcomes Evaluated	Study Quality
Milisen, 2001[70] Belgium Study Design: Before and after study Funding Source(s): Government, Private Industry	Prevention Strategy Used: education of nursing staff; systematic cognitive screening; consultative services by delirium resource nurse, geriatric nurse specialist, or psychogeriatrician; scheduled pain protocol (n=60) Control:; usual care prior to implementation of intervention (n=60)	Inclusion Criteria: admitted to emergency department of one hospital with traumatic fracture of proximal femur and hospitalized in 1 of 2 traumatological nursing units within 24 hrs of surgery; Dutch speaking and verbally testable Exclusion Criteria: multiple trauma, concussion, pathological fractures, surgery occurring more than 72 hours after admission, aphasia, blindness, deafness, fewer than 9 years of formal education Recruitment Method: all patients approached by research nurses within 48 hours after admission	N=120 Median age (yrs): 81 Gender, male (%): 19 Race/ethnicity (%): NR Medical Unit: traumatological wards	Delirium incidence (based on CAM) Duration of delirium Mortality Length of stay	Allocation Concealment: NA Blinding: NA Intention to Treat Analysis (ITT): yes Withdrawals adequately described: NA

Author, Year, Country, Study Design, Funding Source	Prevention Strategy Used, Controls	Inclusion and Exclusion Criteria, Recruitment Method	Patient Characteristics (expressed in means unless otherwise noted)	Outcomes Evaluated	Study Quality
Inouye, 1999[71] Rizzo 2001[72] Inouye 2003[73] Leslie 2005[75] Leslie 2005[75] United States Study Design: controlled clinical trial Funding Source(s): National Institute on Aging and other local non-industry grants	Prevention Strategy Used: multi-component strategy (Elder Life Program); intervention consisted of standardized protocols for the management of six risk factors for delirium: cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration (n=426) Controls: prospectively matched patients (n=426) Note: intervention strategy was implemented by a trained interdisciplinary team, which consisted of a geriatric nurse-specialist, two specially trained Elder Life specialists, a certified therapeutic-recreation specialist, a physical therapy consultant, a geriatrician, and trained volunteers	Inclusion Criteria: at least 70 years old, no delirium at the time of admission, and at intermediate or high risk for delirium at baseline Exclusion Criteria: inability to participate in interviews (because of profound dementia that precluded verbal communication, language barrier, profound aphasia, or intubation or respiratory isolation), coma or terminal illness, hospital stay of 48hours or less, prior enrollment in this study Recruitment Method: all subjects in intervention unit who met the eligibility criteria were enrolled; concurrently, eligible patients from two usual-care units were identified, so subject pool was sufficiently large to permit use of a computerized algorithm designed to match patients according to age within five years, sex, and base-line risk of delirium (intermediate or high)	N=852 Mean age (yrs): 80 Gender, male (%): 39 Race/ethnicity (%): white 87 Medical unit: General medicine	Delirium incidence (defined according to the criteria of the CAM) Total days of delirium No. of episodes of delirium Delirium-severity score Recurrence (two or more episodes)	Allocation Concealment: Not feasible, but a prospective, individual matching strategy was chosen as an alternative to randomization Blinding: none stated Intention to Treat Analysis (ITT): yes Withdrawals adequately described: yes
Lundstrom, 1999[76] Sweden Study Design: prospective case series with 2 historical control case series (see Gustafson, 1991) Funding Source(s): several non-industry grants	Prevention Strategy Used: intervention program - staff education, co-operation between orthopedic surgeons and geriatricians, individual care and planning of rehabilitation, improved ward environment, active nutrition, improved continuity of care and prevention and treatment of complications associated with delirium (n=49) Controls: patients from two studies, one a control and one a medical intervention; all patients were 65 years of age and older consecutively admitted to an orthopedic hospital for femoral neck fracture repair (n=111 and n=103)	Inclusion Criteria: patients operated on for fractured neck of the femur Exclusion Criteria: NR Recruitment Method: patients with hip fractures from the study catchment area admitted to the department in which the orthopedic surgeon and the geriatricians co-operate in the treatment and care of the patients	N=49 (Intervention) Mean age (yrs): 79.7 Gender, male (%): 35 N=111 (Control 1) Mean age (yrs): 79.3 Gender, male (%): 25 N=103 (Control 2) Mean age (yrs): 79.5 Gender, male (%): 27 All Groups: Race/ethnicity (%): NR Medical unit: orthopedics	Diagnosed delirium (based on DSM-III-R criteria).	Allocation Concealment: NA Blinding: NR Intention to Treat Analysis (ITT): NA Withdrawals adequately described: NA

Author, Year, Country, Study Design, Funding Source	Prevention Strategy Used, Controls	Inclusion and Exclusion Criteria, Recruitment Method	Patient Characteristics (expressed in means unless otherwise noted)	Outcomes Evaluated	Study Quality
Wanich, 1992[77] United States Study Design: quasi-experimental Funding Source(s): foundation and government grants	Prevention Strategy Used: nursing staff education, subject orientation, communication with family, mobilization, environmental modifications, caregiver education, medication management, discharge planning (n=135) Controls: nursing care per unit staff (usual care) (n=110)	Inclusion Criteria: age 70 and older, admitted to study medical unit between Sunday noon and Friday noon Exclusion criteria: transferred from another unit within the hospital, admitted for short-stay procedure, admitted only for terminal care Recruitment Method: Consent sought within 24 hours of admission to study unit or control units	N=235 Mean age (yrs): 77 Gender, male (%): NR Race/ethnicity (%): NR Medical unit: non-critical care general medicine units with geriatric clinical specialist nurses in Intervention unit	Diagnosed delirium (based on Delirium Screening Assessment [MMSE#, BPRS#, and clinical exam] with psychiatrist making final diagnosis based on DSM-III) Hospital mortality Length of stay #MMSE=Mini-Mental State Examination BPRS=Brief Psychiatric Rating Scale	Allocation Concealment: NA Blinding: psychiatrist who made final diagnosis blinded to Delirium Screening Assessment Intention to Treat Analysis (ITT): NA Withdrawals adequately described: NA
Gustafson, 1991[78] Sweden Study Design: prospective case series with historical controls Funding Source(s): several foundation grants	Prevention Strategy Used: 1) surgical policy (operate as soon as possible), 2) pre-operative assessment and thrombosis prophylaxis 3) oxygen therapy, 4) anesthetic technique, and 5) post-operative assessment and treatments (n=103) Controls: patients seen in the same orthopedic department approximately 3 years prior to study period (n=111)	Inclusion Criteria: consecutive patients, 65 and older, fractured neck of the femur Exclusion criteria: none stated Recruitment Method: consecutive admissions	N=103 (Intervention) Mean age (yrs): 79.5 Gender, male (%): 27 N=111 (Controls) Mean age (yrs): 79.3 Gender, male (%): 25 Both Groups: Race/ethnicity (%): NR Medical unit: Orthopedic Surgery	Delirium incidence (acute confusion based in DSM-III criteria) Duration of delirium Orthopedic ward stay Mortality	Allocation Concealment: NA Blinding: NR Intention to Treat Analysis (ITT): NA Withdrawals adequately described: NA

Appendix D, Table 4. Primary Prevention Outcomes of Non-Pharmacologic or Mixed Studies

Author, Year	Delirium Incidence/ Prevalence n/N (%)		Delirium Severity		Delirium Duration, days (SD unless noted)		Length of Stay, days (SD unless noted)		Use of Rescue Medications n/N (%)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Randomized trials										
Lundstrom, 2007[55] *Specialized geriatric ward, multi-disciplinary education and multi-component intervention*	56/102 (54.9) p<0.01 Delirium ≥ 1 during hosp. after day 7 18/102 (18.4) p<0.001 Delirious on day of discharge 0/102 p<0.001	73/97 (75.3) Delirium ≥ 1 during hosp. after day 7 50/97 (51.5) Delirious on day of discharge 20/97 (20.6)			5.0 (7.1) p=0.01	10.2 (13.3)	28.0 (17.9) p=0.03 Delirious pts. only 31.4 (19.3) p=0.03	38.0 (40.6) Delirious pts. only 43.6 (42.7)	Sedatives (delirious pts.) 6/39 (15.4) p<0.01 Opioids (delirious pts.) 12/39 (30.8) p<0.01	Sedatives (delirious pts.) 20/48 (41.7) Opioids (delirious pts.) 29/47 (61.7)
Taguchi, 2007[56] *Bright light*	1/6 (16.7) p=0.42	2/5 (40.0)								
McCaffrey, 2006[57] *Music*	2/62 (3.2) p<0.01	36/62 (58.1)								
Lundstrom, 2005[58] *Staff education & multi-component intervention*	63/200 (31.5) p=0.91 Remain delirious on day 7 19/63 (30.2) p<0.01	62/200 (31.0) Remain delirious on day 7 37/62 (59.7) p<0.01					9.4 (8.2) p<0.001	13.4 (12.3)		
Marcantonio, 2001[59] *Proactive geriatrics consultation*	20/62 (32) p=0.04 Severe delirium 7/62 (12) p=0.02 Delirium at discharge 8/62 (13)	32/64 (50) Severe delirium 18/64 (29) Delirium at discharge 12/64 (19)			2.9 (2.0) (per episode) p=NS	3.1 (2.3) (per episode)	5 (2) (median and IQR) p=NS	5 (2) (median and IQR)		

Author, Year	Delirium Incidence/ Prevalence n/N (%)		Delirium Severity		Delirium Duration, days (SD unless noted)		Length of Stay, days (SD unless noted)		Use of Rescue Medications n/N (%)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Non-randomized studies										
Ushida, 2009[60] *Decreased steroids and immediate post-surgical movement with cervical orthosis*	3/38 (7.9) p=0.01	23/81(28.4)								
Vidan, 2009[61] *Multi-disciplinary education & multi-component intervention*	20/170 (11.7) p<0.05	69/372 (18.5)	Based on CAM, range 0-7 4.9 (0.4) p=0.08	Based on CAM, range 0-7 5.3 (1.0)	*Hours* 31.1 (43.0) p=0.73	*Hours* 33.6 (22.0)				
Kratz, 2008[62] *Education & multi-component nursing intervention*	Protocol units (4.7)	Control units (11.0)								
Robinson, 2008;[63] Vollmer 2007[64] *Nursing and nursing assistant education and multi-component intervention*	Protocol 11/80 (13.8) p<0.001	Pre-protocol 30/80 (37.5)								

Author, Year	Delirium Incidence/ Prevalence n/N (%)		Delirium Severity		Delirium Duration, days (SD unless noted)		Length of Stay, days (SD unless noted)		Use of Rescue Medications n/N (%)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Caplan, 2007[65] *Multi-component intervention via volunteers and nursing assistants*	1/16 (6.3) p=0.03	8/21 (38.1)	Based on MDAS (scale not provided) 1.2 p<0.05	Based on MDAS (scale not provided) 5.1	5 (only 1 subject, no SD) p=0.64	12.5 (14.5)	22.5 (9.6) p=0.35	26.8 (17.8)		
Harari, 2007[66] *Pre-op geriatric assessment and post-op follow-through*	Protocol 3/54 (5.6) p=0.04	Pre-Protocol 10/54 (18.5)					11.5 (5.2) p=0.03	15.8 (13.2)		
Naughton, 2005[67] *ER and geriatric unit physician and nurse education & multi-component intervention*	4-month cohort: 35/154 (22.7); p<0.01 9-month cohort: 21/110 (19.1); p<0.001	Baseline 45/110 (40.9)					*Non-delirious pts only* 4- and 9 month cohorts combined (n=208) 8.2	*Delirious pts only* Baseline (n=45) 11.5	*Significant differences from baseline* *4-mo cohort:* Anti-depressants: 29/154 (19%); p<0.05 *9-mo cohort:* Benzo-diazepines: 11/110 (10%); p<0.01 Anti-histamines: 4/110 (4%); p<0.01 Opiates: 25/110 (23%); p<0.01	Benzo-diazepines: 34/110 (31%) Anti-depressants: 11/110 (10%) Anti-histamines: 17/110 (16%) Opiates: 47/110 (43%) Neuroleptics: 12/110 (11%)
Tabet, 2005[68] *Staff education*	12/122 (9.8) p=0.03	25/128 (19.5)								
Wong Tim Niam, 2005[69] *Multi-component intervention recommended by geriatric registrars*	Post-intervention 9/71 (12.7) p=0.01	Baseline period 10/28 (35.7)			Baseline period 5 (2-6) p=0.43	Post-intervention Median (range) 3 (2-4)	Baseline period Median (range) 8 (3-41); p=NS	Post-intervention Median (range) 10 (2-44)		

Author, Year	Delirium Incidence/ Prevalence n/N (%)		Delirium Severity		Delirium Duration, days (SD unless noted)		Length of Stay, days (SD unless noted)		Use of Rescue Medications n/N (%)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Milisen, 2001[70] *Inter-disciplinary education and multi-component intervention*	12/60 (20.0) p=NS	14/60 (23.3)	Post-op Day 1: 2.73 Day 3: 3.82 Day 5: 3.36 Day 8: 1.91 (Total CAM score), p=0.02	Post-op Day 1: 6.92 Day 3: 5.78 Day 5: 6.54 Day 8: 6.0 (Total CAM score)	1 (1) (median and IQR) p=0.03	4 (5.5) (median and IQR)	13 (6.5) (median and IQR) p=NS	16 (5.25) (median and IQR)		
Inouye 1999,[71] Rizzo 2001,[72] Inouye 2003,[73] Leslie 2005[75] Leslie 2005[74] *Inter-disciplinary multi-component intervention*	Episodes 62 p=0.03 First episode 42/426 (9.9) p=0.02	90 First episode 64/426 (15.0)	‡3.85±1.27; p=0.25	3.52±1.44	Total days 105 p=0.02	161	Median 7 days	Median 7 days		
Lundstrom, 1999[76] *Inter-disciplinary education and multi-component intervention*	Post-op 15/49 (30.6) p<0.001 vs. Control 1 (C1); p<0.05 vs. Control 2 (C2) Delirium ≥ 7 days 8/49 (16.3) p<0.01 vs. C1, p=0.09 vs. C2	Post-op C1 68/111 (61.3) C2 49/103 (47.6) Delirium ≥ 7 days Control 1 44/111 (39.6) Control 2 29/103 (29.1)					Ward (orthopedic) stay 12.5; p=NR	Ward (orthopedic) stay C1 17.4 C2 11.6		
Wanich, 1992[77] *Inter-disciplinary education and multi-component intervention*	26/135 (19.0) p=0.61	22/100 (22.0)								
Gustafson, 1991[78] *Multi-component intervention*	Post-op 49/103 (47.6) p<0.05 Severe 7103 (6.8) p<0.0001 More than 7 days 30/103 (29.1)	Post-op 68/111 (61.3) Severe 33/111 (29.7) More than 7 days 44/111 (39.6)					Orthopedic Ward 12.8 (10.4) p<0.01	Orthopedic Ward 20.0 (15.4)		

Appendix D, Table 5: Characteristics of Intensive Care Unit Diagnostic Accuracy Studies

Author, Year Country Funding	Level of Evidence	Inclusion and Exclusion Criteria Recruitment Method	Patient Characteristics	Index Test(s) and Examiner Reference Standard and Examiner	Outcomes Evaluated
Bergeron, 2001[114] CANADA Funding: NR	2	Inclusion: admitted to medical and surgical ICU for >24 hours Exclusion: diagnosis of delirium on admission, comatose or stuporous	N= 93 Mean age (yrs): 62 Gender, male (%): 52 VETERAN (Y/N): N Race/ethnicity (%): NR Medical unit: med/surg ICU Comorbid conditions (list): NR APACHE II 14 (8-21)	ICDSC – ICU physician Diagnosis by consulting board certified psychiatrist	Validation of ICDSC
McNicoll, 2005[115] USA Funding: government, foundation	2	Inclusion: consecutive patients admitted to ICU, ≥65 years Exclusion: no appropriate surrogate, transferred from another ICU, non-English speaking, inability to communicate, intubated, mechanically ventilated, or physically restrained	N= 22 Mean age (yrs): 78 Gender, male (%): 36 VETERAN (Y/N): N Race/ethnicity (%): caucasian 73 Medical unit: ICU Comorbid conditions (list): visual/hearing impairments (38%), history of alcohol use (33%), disability in ADLs (37%), preexisting cognitive impairment (45%) APACHE 25.9 CHARLSON 2.0	CAM-ICU - trained clinician researchers CAM - trained clinician researchers	Sensitivity and specificity of CAM and CAM-ICU
van Rompaey, 2007[120] Belgium Funding: NR	5	Inclusion: non intubated, score of at least 10 on Glasgow Coma Scale, 18 years or older; ICU stay of at least 24 hours before first assessment Exclusion: none stated	N= 172 Mean age (yrs): 60 Gender, male (%): 59 VETERAN (Y/N): N Race/ethnicity (%): NR Medical unit: ICU Comorbid conditions (list): NR APACHE II: 21	NEECHAM – trained nurse researcher CAM-ICU - same nurse researcher	Comparison of NEECHAM with CAM-ICU Length of stay
Hart, 1996[109] USA Funding: institutional grant	4	Inclusion: patients with delirium (from ICU), schizophrenia (inpatient), or depressive illness(inpatient) (all by DSM-III-R criteria) or dementia (outpatient) Exclusion: history of substance abuse, major medical illness, or neurologic disorders	N= 103 (22 with delirium) For Delirium Patients: Mean age (yrs): 62.5 Gender, male (%): 54.5 VETERAN (Y/N): N Race/ethnicity (%): African American 50, caucasian 50 Medical unit: ICU Comorbid conditions (list): NR APACHE: NR	CTD – bachelor's level psychologist technician DSM III-R-psychiatrist	How well CTD performed across 4 populations (delirium, dementia, depression, schizophrenia)

Author, Year Country Funding	Level of Evidence	Inclusion and Exclusion Criteria Recruitment Method	Patient Characteristics	Index Test(s) and Examiner Reference Standard and Examiner	Outcomes Evaluated
Ely, 2001[110] USA Funding: government, foundation	3	Inclusion: admitted to ICU Exclusion: history of severe dementia, psychosis or neurologic disease; patient or family refusal; comatose	N= 38 Mean age (yrs): 60 Gender, male (%): 60 VETERAN (Y/N): N Race/ethnicity (%): caucasian 84, African American 14, Hispanic 2 Medical unit: ICU Comorbid conditions* (list): acute respiratory distress 29%, MI or arrhythmia 16%, CHF 16%, hepatic or renal failure 13%, COPD 11%, GI bleeding 8%, malignancy 5% APAHCE II: 17.1	CAM-ICU – study nurses and intensivists DSM IV – geriatrician, geriatric consult-liaison psychiatrist	Validation of CAM-ICU
Pisani, 2006[111] USA Funding: foundation	3	Inclusion: medical ICU patients, 60 years and older Exclusion: no proxy, patient died during proxy interview, transfer from other ICU; in ICU<24h, non-English speaking	N= 178 Mean age (yrs): 74.2 Gender, male (%): 52 VETERAN (Y/N): N Race/ethnicity (%): non-caucasian 12 Medical unit: ICU Comorbid conditions (list): dementia (29%), disability in ADLs (31%), GI hemorrhage* (16%), respiratory* (51%), neurologic* (2%), sepsis* (17%) APACHE II: 23.4 CHARLSON: 1.9	Chart-based delirium method – trained research nurse CAM-ICU—trained research nurses	Validation of chart-based delirium detection method
Ely, 2001[116] USA Funding: government, foundation	2	Inclusion: medical and coronary ICU patients, mechanically ventilated Exclusion: history of psychosis and neurologic disease, inability to communicate (non-English speaking, deaf, comatose), extubated before assessment, previously enrolled in the study, refusal to participate	N= 96 Mean age (yrs): 55.3 Gender, male (%): 47.9 VETERAN (Y/N): N Race/ethnicity (%): caucasian 79.2, black 19.8, Hispanic 1.0 Medical unit: ICU Comorbid conditions* (list): acute respiratory distress 35%, cancer 15%, myocardial infarction or arrhythmia 9%, hepatic or renal failure 9%, CHF 6%, COPD 6%, GI bleeding 5%, drug overdose 3%, other 12% APACHE II: 22.9	CAM-ICU – critical care study nurses DSM IV – geriatrician delirium expert, board certified geriatric consult-liaison psychiatrist, or neuropsychologist	Validation of CAM-ICU Length of stay
Spronk, 2009[121] Netherlands Funding: NR	5	Inclusion: ICU stay >48 hours Exclusion: preexisting neurocognitive dysfunction, documented dementia, language barriers or deafness, active psychiatric disorder, severe neurologic disorder	N= 46 Mean age (yrs): 73 Gender, male (%): 65 VETERAN (Y/N): N Race/ethnicity (%): NR Medical unit: ICU Comorbid conditions (list): NR APACHE II: 18	Clinical judgment – ICU nurses and physicians CAM-ICU - research nurses	Validation of clinical judgment Length of stay Mortality

Author, Year Country Funding	Level of Evidence	Inclusion and Exclusion Criteria Recruitment Method	Patient Characteristics	Index Test(s) and Examiner Reference Standard and Examiner	Outcomes Evaluated
van Eijk, 2009[122] Netherlands Funding: NR	1	Inclusion: all (adult) admissions to ICU (medical 24%, surgical 25%, cardiothoracic surgical 29%, neurological/neurosurgical 22%) Exclusion: deeply sedated, comatose, deaf; did not speak Dutch or English, did not consent	N= 126 Mean age (yrs): 62.4 Gender, male (%): 72 VETERAN (Y/N): N Race/ethnicity (%): NR Medical unit: ICU Comorbid conditions (list): NR APACHE II: 20.9	CAM ICU – trained ICU study nurses ICDSC – patient's bedside ICU nurse Diagnostic impression –critical care intensivist, fellow, or resident DSM IV - psychiatrist, neurologist, geriatrician	Validation of CAM-ICU, ICDSC, and physician impression
Guenther, 2010[123] Germany Funding: government, industry	2	Inclusion: all admissions to ICU Exclusion: coma, acute stroke, refusal, non-Germanspeaking	N= 54 Mean age (yrs): 67 Gender, male (%): 69 VETERAN (Y/N): N Race/ethnicity (%): NR Medical unit: ICU Comorbid conditions* (list): Abdominal surgery 13%, vascular surgery 6%, urology 2%, lung surgery 1%, cardiac surgery 23%, trauma 4%, ear/nose/throat surgery 2% APACHE: NR	CAM-ICU Flowsheet – intensivist, trained medical student DSM IV - psychiatrist	Validation of CAM-ICU Flowsheet
Plaschke, 2008[117] Germany Funding: foundation	5	Inclusion: admitted to ICU after elective surgery or after emergency, age 18 or older Exclusion: profound hearing or vision impairment, non-German speaking, coma or unconscious	N= 174 Mean age (yrs): 62.4 Gender, male (%): 70.1 VETERAN (Y/N): N Race/ethnicity (%): NR Medical unit: ICU Comorbid conditions* (list): pancreas resection 32%, GI 21%, cardiorespiratory 19%, urology/renal failure 10%, metabolic disease 9%, polytrauma 4%, other 5% APACHE II: 25 p/m	ICDSC - trained nurses CAM-ICU - physician researcher NOTE: study compared agreement of these 2 tools	Agreement of the ICDSC and CAM-ICU Length of stay Mortality
Shyamsundar, 2009[118] India Funding: NR	5	Inclusion: admitted to medical or cardiac ICU, age 13 or older Exclusion: unable to speak, intubated, refused consent	N= 120 Mean age (yrs): 54.9 Gender, male (%): 72.5 VETERAN (Y/N): N Race/ethnicity (%): NR Medical unit: ICU Comorbid conditions (list): NR APACHE: NR	MDAS – junior resident ICD-10 (International Classification of Diseases, 10th revision) – psychiatrist (unclear if all patients were evaluated by psychiatrist)	Validation of MDAS Interrater reliability

Author, Year Country Funding	Level of Evidence	Inclusion and Exclusion Criteria Recruitment Method	Patient Characteristics	Index Test(s) and Examiner Reference Standard and Examiner	Outcomes Evaluated
Koolhoven, 1996[119] UK Funding: NR	5	Inclusion: admitted after elective cardiac surgery, >21 years of age Exclusion: refused, death	N= 15 Mean age (yrs): 63 Gender, male (%): 80 VETERAN (Y/N): N Race/ethnicity (%): NR Medical unit: ICU Comorbid conditions (list): NR APACHE: NR	Observation checklist (based on DRS) - study physicians DSM III R - unclear	
Lin, 2004[113] China Funding: government	1	Inclusion: in ICU, mechanically ventilated Exclusion: history of dementia, psychosis, mental retardation, other neurologic disease; receiving antipsychotics or high dose morphine or midazolam; under general anesthesia or heavily sedated, refused	N= 102 Mean age (yrs): 73.4 Gender, male (%): 53 VETERAN (Y/N): N Race/ethnicity (%): NR Medical unit: ICU Comorbid conditions* (list): pneumonia (31%), lung disease (24%), stroke (11%), cancer (8%), CHF (5%), GI disease (5%), diabetes or metabolic disorder (5%), myocardial infarction (3%), drug intoxication (3%) APACHE III: 64.9	CAM-ICU - 2 research assistants DSM IV - psychiatrists	Validation of CAM-ICU Mortality Interrater reliability
Luetz, 2010[112] Germany Funding: NR	1	Inclusion: newly admitted to ICU after surgery, age ≥ 60, LOS at least 24h Exclusion: preexisting psychosis, dementia, depression, non-German speaking, inability to communicate	N= 156 Mean age (yrs): 69.8 Gender, male (%): 55 VETERAN (Y/N): N Race/ethnicity (%): NR Medical unit: ICU Comorbid conditions* (list): general surgery (39%), cardiac (25%), trauma (16%), gynecologic (9), urologic (4%), otorhinolaryngological (4%), vascular (2%), oral (1%) APACHE II: 18	CAM-ICU, Nu-DESC, DDS – trained physicians and nurses DSM IV – board-certified psychiatrist or intensivist	Validation of CAM-ICU, Nu-DESC, and DDS Interrater reliability Length of stay Discharge disposition

*ICU admission diagnosis

APACHE = Acute Physiology and Chronic Health Evaluation; NR = not reported; ADLs = Activities of Daily Living;
CAM-ICU = Confusion Assessment Method – Intensive Care Unit; CAM = Confusion Assessment Method; CTD = Cognitive Test for Delirium; DDS = Delirium Detection Score; DSM = Diagnostic and Statistical Manual of Mental Disorders; ICDSC = Intensive Care Delirium Screening Checklist; MDAS = Memorial Delirium Assessment Scale; NEECHAM = Neelon and Champagne Confusion Scale; Nu-DESC: Nursing Delirium Screening Scale