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Delirium: Screening, Prevention, and Diagnosis – A Systematic Review of the Evidence

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PREFACE

Health Services Research & Development Service's (HSR&D's) Evidence-based Synthesis Program (ESP) was established to provide timely and accurate syntheses of targeted healthcare topics of particular importance to Veterans Affairs (VA) managers and policymakers, as they work to improve the health and healthcare of Veterans. The ESP disseminates these reports throughout VA.

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- develop clinical policies informed by evidence,
- guide the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures, and
- set the direction for future research to address gaps in clinical knowledge.

In 2009, the ESP Coordinating Center was created to expand the capacity of HSR&D Central Office and the four ESP sites by developing and maintaining program processes. In addition, the Center established a Steering Committee comprised of HSR&D field-based investigators, VA Patient Care Services, Office of Quality and Performance, and Veterans Integrated Service Networks (VISN) Clinical Management Officers. The Steering Committee provides program oversight, guides strategic planning, coordinates dissemination activities, and develops collaborations with VA leadership to identify new ESP topics of importance to Veterans and the VA healthcare system.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP Coordinating Center Program Manager, at nicole.floyd@va.gov.

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TABLE OF CONTENTS

TABLES

FIGURES

Return to Contents

EVIDENCE REPORT

INTRODUCTION

This review was undertaken to evaluate the effectiveness of screening for delirium in adult inpatients, the effectiveness of strategies employed to prevent delirium in acute elderly inpatients, and the comparative diagnostic accuracy of tools used to detect delirium in elderly medical, surgical, and ICU patients.

For this review, we were careful to make the important distinction between screening for delirium (testing all patients for delirium without a prior index of suspicion) and diagnosis of delirium (testing those patients for whom there is already some suspicion of delirium).

BACKGROUND

Delirium is a common syndrome, characterized by the acute onset of altered mental status, hallmarked by difficulty sustaining attention and a fluctuating course, and frequently causing patients, families, and health care providers considerable distress. There have been wide variations in the reported incidence of delirium in medical inpatients, largely due to differences in setting, patient population, and methodology. It has been estimated that 10-30% of patients admitted to the hospital develop delirium;[9,10] this percentage can increase significantly in at-risk populations, including frail elderly patients (estimated at 60%),[11] post-surgical elderly patients (estimated as high as 89%),[12] or ICU patients (estimated at 41%).[13]

Delirium has been associated with multiple serious outcomes in medically ill patients, including increased morbidity, length of stay, healthcare costs, institutionalization, and mortality.[2,3,14-16] Delirium is often significantly under-recognized by healthcare providers and can frequently be difficult to resolve.[5,6,17,18] Several brief "bedside" questionnaires and checklists exist that can detect delirium earlier and among those with milder symptoms. Efforts to prevent the development of delirium in those at risk have been advocated.[3,6] Medications (including sedatives, narcotics, and anticholinergic drugs), diseases and intercurrent illnesses (e.g., stroke, infection, shock, anemia), surgical procedures (especially orthopedic and cardiac surgery), and environmental factors (e.g., use of a bladder catheter, pain, and emotional stress) are all precipitating factors for delirium development.[6,7] Therefore, identifying and implementing effective strategies to prevent and detect delirium could improve clinical outcomes and resource utilization. Suggested strategies to prevent delirium include avoidance of psychoactive medications, pharmacologic interventions to decrease risk, and single- or multi-component non-pharmacologic interventions (including use of music, mobilization, fluid and nutrition management, and orientation and cognitive stimulation).[4,6,7]

METHODS

TOPIC DEVELOPMENT

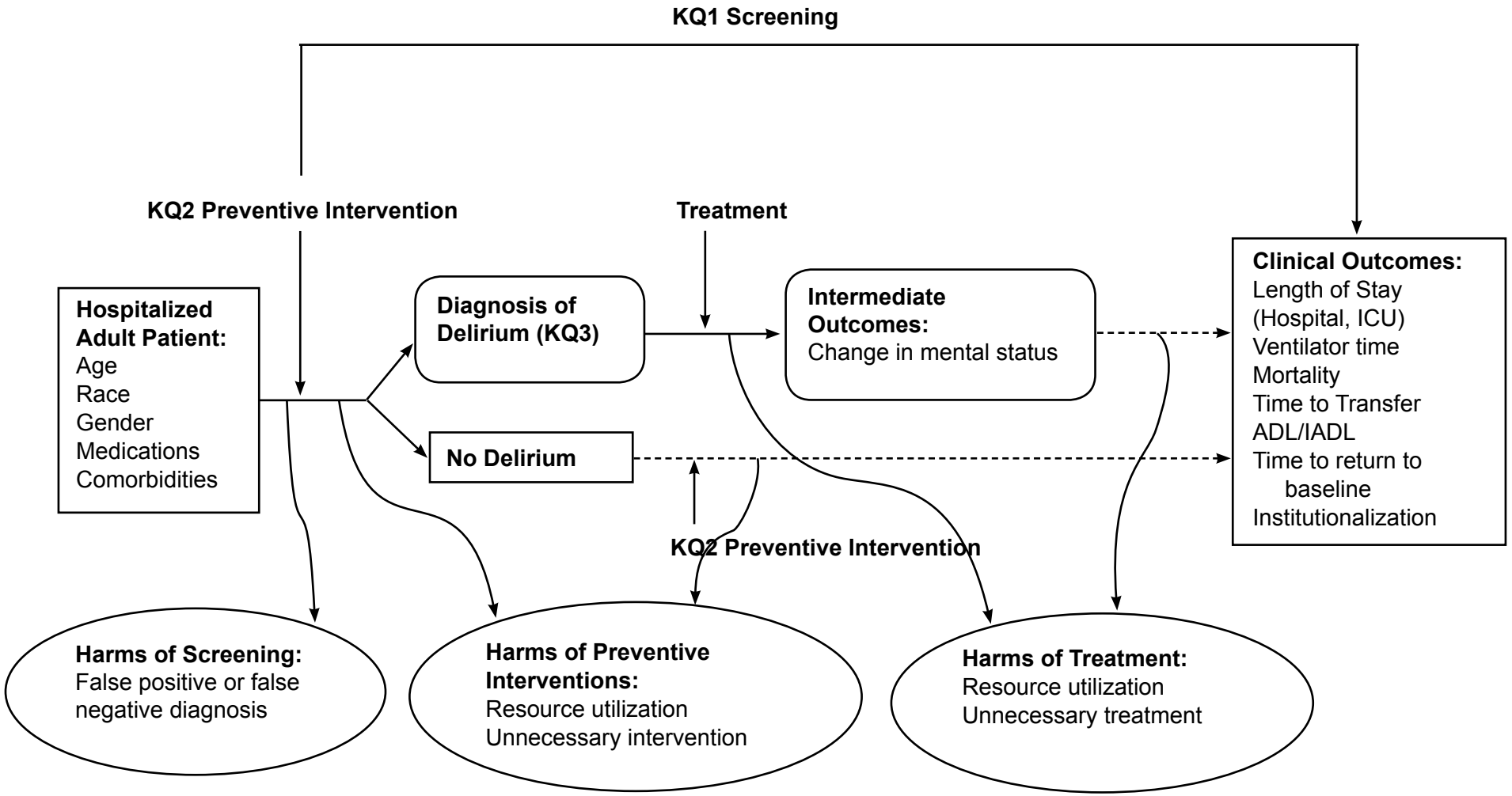
This project was nominated by Nancy Schmid, ADPNS, a Nurse Executive at Syracuse VA Medical Center, with input from a technical expert panel of clinicians, researchers, and administrators.

The final key questions are:

1. What is the *effectiveness* of *screening* for delirium in adult inpatients?
   a. Do these results vary by medical unit, age, gender or comorbid conditions?
   b. Does screening for delirium improve clinical outcomes?
2. What are the *effectiveness and harms* of delirium *prevention* strategies in acute elderly inpatients?
   a. Do these results vary by medical unit, age, gender or comorbid conditions?
3. What is the comparative *diagnostic accuracy* of the tools used to detect delirium:
   a. In elderly medical and surgical inpatients?
   b. In elderly medical or surgical intensive care unit (ICU) inpatients?

An analytic framework (Figure 1) was developed to depict the potential pathway of a hospitalized adult patient. This report will focus on the outcomes and harms associated with screening (Key Question #1), preventive interventions (Key Questions #2), and diagnosis (Key Question #3).

Figure 1. Analytic Framework



Return to Contents

SEARCH STRATEGY

We searched MEDLINE, CINAHL, and PsycINFO from 1950 to November 2010 using standard search terms (Appendix A). We limited the search to peer-reviewed articles involving human subjects and published in the English language. Additional citations were identified from reference lists and Technical Expert Panel members.

STUDY SELECTION

Physicians, nurses, and research assistants trained in the critical analysis of literature assessed for relevance the abstracts of citations identified from literature searches. Full-text articles of potentially relevant abstracts were retrieved for further review. A Study Selection Form (Appendix B) was used to guide this review.

Specific exclusion criteria for the screening and diagnosis questions were as follows:
1) Non-English publication
2) Population <16 yrs old
3) Alcohol-related delirium
4) Not hospitalized patients (nursing home or similar was excluded)
5) No reference standard (DSM III, III-R, or IV)
6) Index test and reference standard performed by same individual
7) Case series (<10 patients), case report, editorial, letter
8) Not patients with delirium
9) No outcomes of interest
10) Not a screening or diagnosis study

Specific exclusion criteria for the prevention question were as follows:
1) Non-English publication
2) Population <16 years old
3) Nursing home residents (or mixed hospital/nursing home if unable to get results of hospital only)
4) Case series, case report, editorial, letter
5) Not about delirium prevention

DATA ABSTRACTION

Study characteristics, patient characteristics, and outcomes were extracted and evidence and outcomes tables, organized by key question, were created under the supervision of the Principal Investigator, a geriatric psychiatrist.

QUALITY ASSESSMENT

We assessed study quality of randomized trials of prevention strategies (Key Question 2) according to the following criteria: 1) adequate allocation concealment, 2) blinding of key study personnel, 3) analysis by intention-to-treat, and 4) reporting of number of withdrawals/dropouts by group assignment.[19] Studies were rated as good, fair, or poor quality. A rating of good

generally indicated that the trial reported adequate allocation concealment, blinding, analysis by intent-to-treat, and reasons for dropouts/attrition were reported. Studies were generally rated poor if the method of allocation concealment was inadequate or not defined, blinding was not defined, analysis by intent-to-treat was not utilized, and reasons for dropouts/attrition were not reported and/or there was a high rate of attrition.

Study quality of studies reported for Key Question 3 (studies of diagnostic accuracy) was assessed using the method described in the Rationale Clinical Examination series.[8] Briefly, studies are designated as Level of Evidence 1 if they present an independent, blinded comparison with a criterion standard in a large number (defined as 100 or more patients in the delirium diagnosis review) of consecutive individuals suspected of having the target condition or a Level of Evidence 2 if they meet all the criteria for Level 1 but enroll fewer than 100 patients. Level of Evidence 3 studies are similar to Level 1 or Level 2 studies but do not enroll patients consecutively. Studies with a non-independent comparison with the criterion standard and that enroll (at least in part) patients who obviously have the target condition are designated as Level of Evidence 4. Studies with a reference test of questionable validity are designated Level of Evidence 5.

DATA SYNTHESIS

We constructed evidence tables showing the study characteristics and results for all included studies, organized by key question. We critically analyzed studies to compare their characteristics, methods, and findings. Pooled analyses were performed, where feasible, for studies of prevention strategies. All other data were narratively summarized.

RATING THE BODY OF EVIDENCE

We assessed the overall quality of evidence for randomized trials of prevention strategies (Key Question #2) using the method reported by Owens et al.[20] Briefly, for each outcome evaluated, the strength of the evidence was assessed based on: (1) risk of bias; (2) consistency; (3) directness; and (4) precision. Based on these four domains, the overall evidence was rated as: (1) high, meaning high confidence that the evidence reflects the true effect; (2) moderate, indicating moderate confidence that further research may change our confidence in the estimate of effect and may change the estimate; (3) low, meaning there is low confidence that the evidence reflects the true effect; and (4) insufficient, indicating that evidence either is unavailable or does not permit a conclusion. Due to heterogeneity in the interventions evaluated, we did not rate the overall strength of evidence for the non-randomized trials.

PEER REVIEW

A draft version of this report was reviewed by technical experts and VA clinical leadership. Their comments and our responses are presented in Appendix C.

RESULTS

LITERATURE FLOW

For the screening question, we identified 1,889 abstracts and excluded 1,778. We reviewed the full text of 111 references and none met inclusion criteria.

For the prevention question, we identified 1,175 abstract and excluded 947. Of 228 full text articles reviewed, 31 met eligibility criteria. We added 8 references from hand-searching for a total of 39 included references. In addition to our literature search, we identified one recent Cochrane systematic review of delirium prevention[21] and a recent National Institute for Health and Clinical Excellence (NICE) guideline on diagnosis, prevention, and management of delirium.[7,22] Five of the six randomized controlled trials included in the Cochrane review are included in our analysis. The sixth trial, a study of prophylactic citicoline (a psychostimulant) versus placebo, was published in Spanish language and was therefore not eligible for our review. The authors reported no difference in delirium incidence.[23]

The NICE guideline cited seven studies of pharmacologic prevention strategies, five studies of non-pharmacologic strategies, and eight studies of multi-component interventions. Six of the pharmacologic studies, one of the non-pharmacologic studies, and seven of the multi-component studies met our inclusion criteria and are included in our analysis. The remaining studies were either not conducted in a hospital setting or did not provide data on outcomes of interest.

For the question about diagnostic accuracy, our search was limited to studies of patients admitted to intensive care units. We identified 76 abstracts and excluded 40 of those. Of 36 full text articles reviewed, 15 met inclusion criteria. Figures 2, 3, and 4 present the literature search results.

Figure 2. Flow Diagram – Delirium Screening Studies

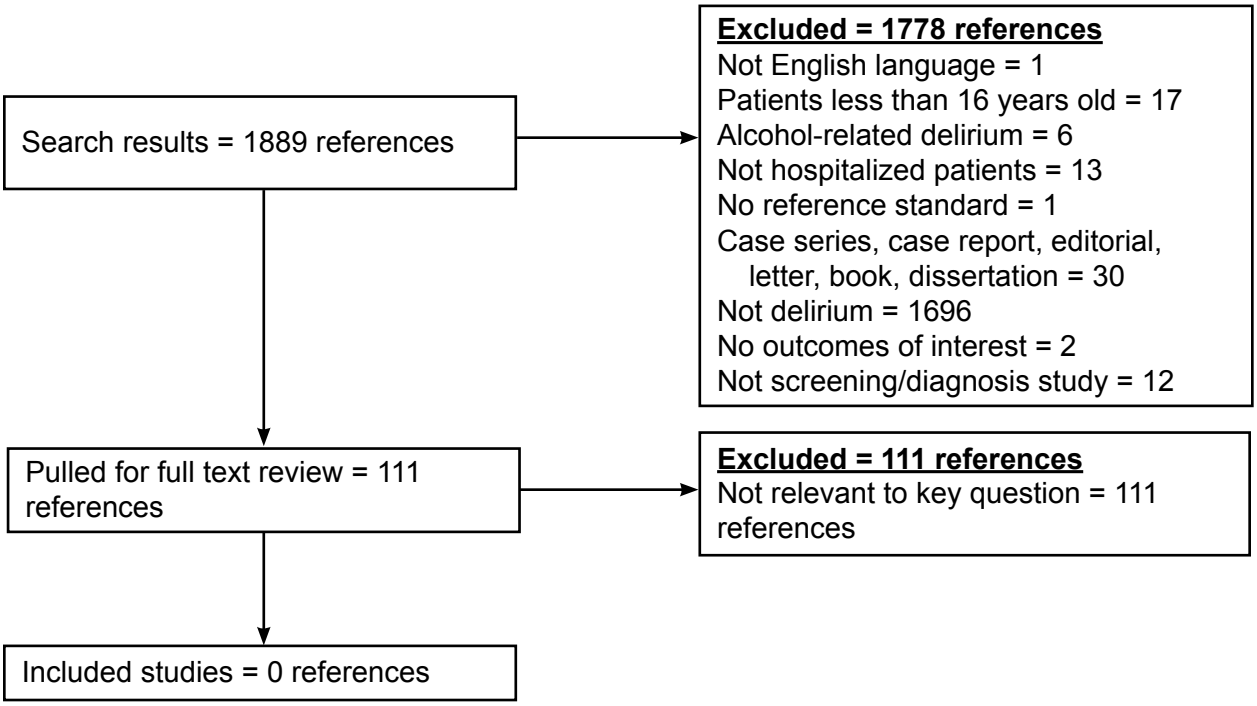


Figure 3. Flow Diagram – Delirium Prevention Studies

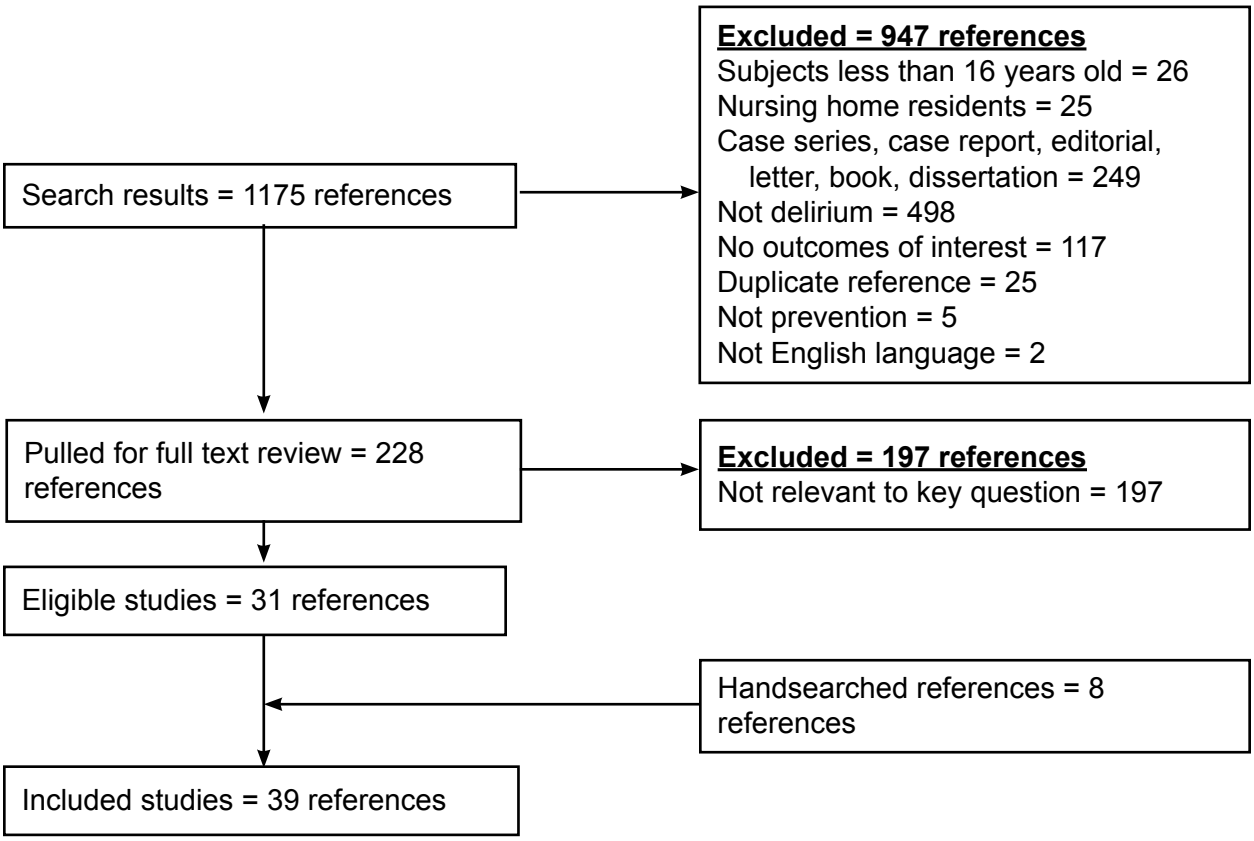
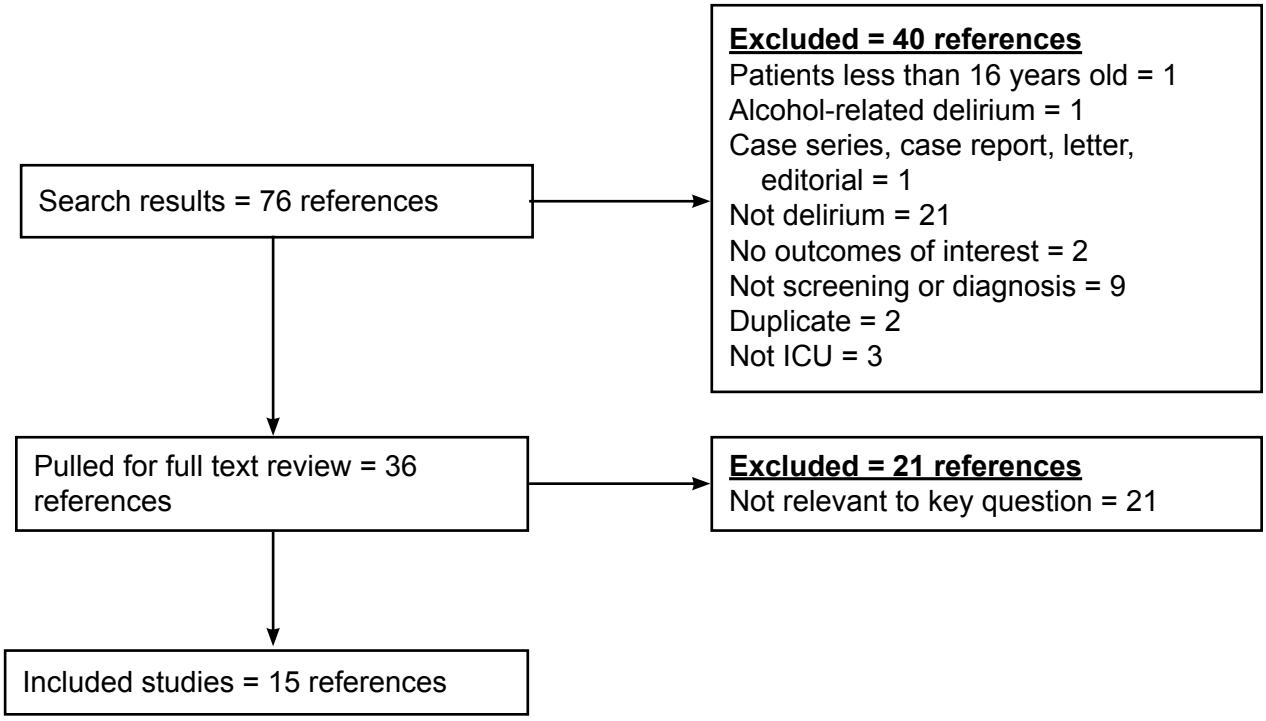


Figure 4. Flow Diagram – Delirium ICU Diagnosis Studies



KEY QUESTION #1. What is the effectiveness of screening for delirium in adult inpatients?

Screening for a disease or condition is warranted if the disease is serious, if treatment before symptoms are evident reduces morbidity and mortality, and if the prevalence of preclinical disease is high among the population screened.[24] In addition, the screening test should identify most or all with the condition, be cost effective and ethical, be easy to administer, and impose minimal discomfort on patients. The test must also be reliable, valid, and reproducible.[25]

Based on the criteria above, screening for delirium may be appropriate. However, we did not identify any studies comparing patient outcomes in hospitalized (including intensive care unit) patients randomly assigned to screening or no screening for delirium.

In the absence of direct evidence we look for indirect links between screening and outcomes. To indirectly link screening and outcomes, we would need evidence that 1) patients with delirium have worse outcomes, 2) systematic screening would improve detection of delirium, 3) treatments for detected delirium are effective, particularly if delirium can be detected early, and 4) harms associated with screening are minimal. A systematic review for this evidence is beyond the scope of this report. We report results from recent existing systematic reviews where available.

Outcomes in Patients with Delirium

A 2006 systematic review reported outcomes from 19 study cohorts.[26] Study design, diagnostic method, patient selection criteria, comorbid conditions, length of follow-up, outcome measurement, and adjustment (or lack of adjustment) for potential confounders varied among the studies making conclusions difficult. Overall, there appeared to be increased mortality in patients with delirium. Results for hospital length of stay, resolution of symptoms at discharge, institutionalization at discharge, and functional ability at discharge were less consistent.

Improved Detection

If all hospitalized patients or all patients at increased risk were screened for delirium, detection would be expected to increase. However, we did not identify any systematic reviews on detection rates with screening.

Treatment

A search of the literature identified several recent systematic reviews that focused on treatment. A 2007 Cochrane review included data from 3 randomized trials that compared antipsychotic medications used to treat delirium.[27] No differences in patient outcomes or adverse events were found between low-dose haloperidol, risperidone, and olanzapine. A second review included 14 studies, 9 single-agent and 5 comparative.[28] None of the studies included a placebo control group and the total sample size was 448. Although most subjects experienced improvements in delirium severity, without a blinded placebo comparison group it is impossible to determine the role of the study medication in the observed improvement. Few serious adverse events were reported. A third review included 4 randomized studies of pharmacologic management.[29] The conclusions were similar. A fourth review included non-pharmacological and pharmacological treatments.[30] Regarding non-pharmacological approaches, the authors noted that few studies have focused on

the efficacy of cognitive, emotional, or environmental interventions although they are widely used. They also noted the paucity of high-quality randomized trials of pharmacological interventions

Harms

No systematic reviews have identified harms associated with screening. Potential harms include misclassification resulting in patients either receiving unnecessary treatment or failing to receive potentially beneficial treatment. There is also the potential for psychological harm for the patient and their family when patients are misclassified. Screening tools, such as the Confusion Assessment Method (CAM), are not invasive and require little of the patient's or provider's time or effort. Although cost-effectiveness is beyond the scope of this review, costs to the health care system associated with administering and following up on screening test results should be considered.

Recommendations of Others

Despite the lack of direct evidence of a benefit of screening, some organizations have developed guidelines that recommend screening of patients or targeted screening of patients considered at risk for delirium. The 2010 National Institute for Health and Clinical Excellence (NICE) guideline on diagnosis, prevention, and management of delirium recommends assessment of risk factors for delirium in all patients when they first present to a hospital and observation of people admitted to a hospital at every opportunity for changes in the risk factors for delirium.[7,31] Risk factors cited include age 65 and older, cognitive impairment (past or present) and/or dementia, current hip fracture, and severe illness (defined as a clinical condition that is deteriorating or at risk of deteriorating). The recommendation is based on low and moderate quality evidence from prospective cohort studies. Guidelines developed by the Delirium Guidelines Development Group (Switzerland) call for "routine screening of cognitive functions and delirium, whenever possible, using standardized instruments," notably the Mini-Mental State Examination (MMSE) or Blessed Orientation-Memory-Concentration (BOMC) tests on admission and the CAM during the hospital stay. Particular emphasis was given to systematic screening in at-risk patients. The authors noted the relative lack of evidence supporting the consensus statements.[32] The British Geriatrics Society guidelines include a recommendation to identify all patients over 65 years with cognitive impairment on admission.[33] Delirium should be considered in patients with cognitive impairment and at high risk due to severe illness, dementia, fracture of the femoral neck, and visual and hearing impairment. Serial assessments are recommended in those patients to help detect the new development of delirium. This recommendation was based on evidence from high quality systematic reviews or cohort studies or extrapolated evidence from meta-analyses, systematic reviews, or randomized trials. The Australian clinical practice guideline on management of delirium recommends establishment of a structured process for screening and diagnosis of delirium in all health care settings.[25] The recommended process includes assessment of risk of delirium and cognitive function at admission with repeat testing of high risk patients (age 70 or older, pre-existing cognitive impairment, severe medical illness, depression, abnormal sodium, and visual impairment) and further assessment for delirium and/or referral if there is a decline in the cognitive assessment score. The recommendations were based on expert opinion. Clinical practice guidelines from the American College of Critical Care Medicine of the Society of Critical Care Medicine recommend routine assessment for the presence of delirium,

including ICU patients.[34] The recommendation was graded B (defined as methods strong, results inconsistent, prospective randomized controlled trials with heterogeneity present).

Key Question 1a. Do these results vary by medical unit, age, gender or comorbid conditions?

We did not find any direct evidence that screening is effective regardless of the medical unit, age or gender of the patients, or their comorbid conditions.

Key Question 1b. Does screening for delirium improve clinical outcomes?

We did not find any evidence that screening for delirium improves clinical outcomes in hospitalized (including ICU) patients.

Conclusions

We identified no randomized-controlled trials of screening for delirium in hospitalized patients. We identified several studies that have compared the diagnostic accuracy of a screening tool to an established reference standard (validation studies). Most of these reports focused on selected subsets of hospitalized patients who were at high risk for delirium. Results from those studies are reported in Key Question 3. In addition, there have been many application studies (i.e., evaluating patients at admission and during their hospital stay and reporting on prevalent [present at the time of admission] and incident [developed during hospitalization] cases of delirium). A recent systematic review summarizes validation, adaptation, translation, and application studies for the CAM.[35]

Unfortunately, these types of studies do not address the question of whether screening for delirium in asymptomatic individuals improves patient outcomes nor do they directly assess the potential harms associated with universal screening. Therefore, the available evidence is insufficient to make recommendations about the net benefit of delirium screening among all hospitalized patients or patients admitted to intensive care units.

KEY QUESTION #2. What are the effectiveness and harms of delirium prevention strategies in acute elderly inpatients?

Predisposing and precipitating factors for delirium have been well documented.[4,6,36] Predisposing factors include poor nutrition, dehydration, alcohol or drug abuse, medication use (especially use of sleep medications, narcotic pain relievers, anticholinergics, sedative hypnotics, anti-depressants, Parkinson's disease treatments, anti-convulsants, muscle relaxants, and allergy medications), impaired vision or hearing, sleep deprivation, and low level of activity. Precipitating factors include infection, alcohol or drug withdrawal, emotional stress, multiple medical procedures, pain, and electrolyte disturbances. Prevention strategies typically target one or more of these factors.

Summary of Studies for Key Question 2

The study design, population and study characteristics and quality and outcomes evaluated for each of the included studies are presented in Table 1 and Appendix D, Tables 1 and 3.

Study design and location

Thirty-nine unique studies on prevention of delirium enrolling between 15 and 1059 subjects met inclusion for Key Question 2. A total of 7935 subjects were enrolled in these 39 studies.

Twenty studies evaluated pharmacologic methods for preventing delirium; sixteen of these were randomized,[13,37-51] while four were non-randomized studies.[12,52-54] Five studies evaluated cholinesterase inhibitors,[12,40,45,47,54] while four examined anesthesia,[39,41,48,51] three examined analgesic agents, [13,43,53] four examined antipsychotic medications, [38,44,46,50] and one each examined melatonin,[37] benzodiazepines,[49] post-operative sedation,[42] and a lipid-lowering agent.[52]

Nineteen studies (in 24 publications) evaluated non-pharmacologic or mixed methods of preventing delirium; five of these were randomized[55-59] and fourteen were non-randomized.[60-78] The majority of these studies evaluated multi-component interventions, often combined with staff education.[55,58-67,69-78] The multi-component interventions varied greatly and included such components as geriatric consultation, individual care planning, focused prevention of infection, improving mobility, frequent orientation, bowel and bladder care regimens, insomnia protocols, adequate pain management, minimizing psychoactive or sedating medications, and maintaining adequate hydration and nutrition, among others. Other non-pharmacologic studies examined bright light therapy,[56] the use of music,[57] or the use of staff education alone[68] as strategies for preventing delirium.

Of the 39 prevention studies of delirium,16 were conducted in Europe, 14 in the United States, 4 in Japan, 2 in Australia, , 2 in Canada and 1 in Thailand.

Table 1. Summary of Study Baseline Characteristics for Delirium Prevention Studies

Characteristic	Mean (range) *Unless otherwise noted*	Number of trials reporting
Total number of patients evaluated	7935 (15 to 1059)	39
% of patients (n/N) in randomized pharmacologic intervention studies	28 (2245/7935)	16
% of patients (n/N) in non-randomized pharmacologic intervention studies	17 (1311/7935)	4
% of patients (n/N) in randomized non-pharmacologic intervention studies	11 (866/7935)	5
% of patients (n/N) in non-randomized non-pharmacologic intervention studies	44 (3513/7935)	14
Age of subjects, years	78 (58 to 85)	33
Gender, male, %	44 (19 to 100)	34
Race/ethnicity, white, %	91 (87 to 98)	5
Orthopedics/orthopedic surgery, % of patients (n/N)	33 (2626/7935)	15
Cardiac surgery, % of patients (n/N)	19 (1481/7935)	5
Other surgery, % of patients (n/N)	8 (673/7935)	8
Internal medicine/geriatrics/other, % of patients (n/N)	40 (3155/7935)	11
Studies conducted in the US/Canada, % of patients (n/N)	53 (4253/7935)	16
Studies conducted in Europe, % of patients (n/N)	40 (3161/7935)	16
Studies conducted in Asia/Australia, % of patients (n/N)	7% (521/7935)	7

Patient characteristics

One of the included studies enrolled U.S. veterans.[41] The mean age of the patients included in the 33 prevention studies that reported age was 78 years (range 58 to 85). Twenty-one studies enrolled only patients age 65 or greater. Men comprised 44% of subjects (range 18%-100) in the 34 studies that reported gender. Only five studies reported racial or ethnic characteristics;[38,41,47,59,71] the vast majority of subjects in those five studies were Caucasian (91%, range 87% to 98%). Twenty-eight of the studies involved patients on post-surgical units,[13,37-57,59,60,66,69,70,76] ten involved patients on medicine wards,[12,58,61,63,65,67,68,71,77,78] and one involved patients on medical-surgical units.[62]

Outcome measures

Outcomes reported varied widely between delirium prevention studies included in this report (Appendix D, Tables 2 and 4). All reported delirium incidence, with rates of delirium ranging from 11% to 88.9% in controls. Nine studies reported data regarding delirium severity. Fourteen studies reported data on delirium duration. Twenty-two studies reported data on hospital length of stay. Seven studies reported data regarding use of rescue medications.

Study quality

Most included studies assessing prevention measures utilized methods to reduce sources of bias (Appendix D, Tables 1 and 3). However, 11 studies did not report clear allocation concealment when concealment was possible. Thirteen studies did not utilize an intention-to-treat analysis (or were unclear in reporting) in studies where this would have been possible. Most studies adequately reported withdrawals from the study when this was appropriate, but three studies that would have been appropriate to report withdrawals did not do so.

Effectiveness

Pharmacologic Studies

Twenty studies evaluated pharmacologic interventions (Table 2, Appendix D, Tables 1 and 2). Most interventions were only assessed in single studies that were small in size. All but two studies[12,37] involved post-surgical patients. While all studies reported incidence, 6 reported a measure of delirium severity, 7 reported delirium duration, 11 reported length of stay, and 5 reported use of rescue medications (Appendix D, Table 2). Table 2 lists studies by intervention and provides incidence/prevalence data and relative risks.

Table 2: Incidence of Delirium - Pharmacologic Prevention Studies

	Study	Study Type/Patients	Intervention Control	Delirium Incidence/ Prevalence % (n/N)	Relative Risk [95% Confidence Interval]
Cholinesterase Inhibitors	Liptzin, 2005[47]	RCT/orthopedic	Donepezil Placebo	21 (8/39) 17 (7/41)	1.20 [0.48 to 3.00]
	Sampson, 2007[45]	RCT/orthopedic	Donepezil Placebo	11 (2/19) 36 (5/14)	0.29 [0.07 to 1.30]
	Gamberini, 2009[40]	RCT/cardiac surgery	Rivastigimine Placebo	32 (18/56) 30 (17/57)	1.08 [0.62 to 1.87]
	Dautzenberg, 2004[12]	Non-randomized/ geriatric medicine	Rivastigmine No Rivastigmine	46 (5/11) 89 (26/29)	0.51 [0.26 to 0.98]
	Savage, 1978[54]	Non-randomized/ elective surgery	Physostigmine No Physostigmine	9 (4/45) 43 (29/68)	0.21 [0.08 to 0.55]
Typical Antipsychotics	Kalisvaart, 2005[46]	RCT/orthopedic	Haloperidol Placebo	15 (32/212) 17 (36/218)	0.91 [0.59 to 1.42]
	Kaneko, 1991[50]	RCT/gastrointestinal	Haloperidol Placebo	11 (4/38) 33 (13/40)	0.32 [0.12 to 0.91]
Atypical Antipsychotics	Larsen, 2010[38]	RCT/orthopedic	Olanzapine Placebo	14 (28/196) 40 (82/204)	0.36 [0.24 to 0.52]
	Prakanrattana, 2007[44]	RCT/cardiac surgery	Risperidone Placebo	11 (7/63) 32 (20/63)	0.35 [0.16 to 0.77]
Analgesia	Mouzopolous, 2009[43]	RCT/orthopedic	Fascia iliaca compartment block Placebo	11 (11/102) 24 (25/105)	0.45 [0.24 to 0.87]
	Williams-Russo, 1992[13]	RCT/orthopedic	Continuous epidural Continuous intravenous analgesia	38 (10/26) 44 (11/25)	0.87 [0.45 to 1.69]
	Del Rosario, 2008[53]	Non-randomized/ orthopedic	Patient controlled, femoral nerve Intravenous	8 (4/49) 42 (21/50)	0.19 [0.07 to 0.53]
Anesthesia	Papaioannou, 2005[48]	RCT/elective surgery	Regional (spinal or epidural) General	16 (3/19) 21 (6/28)	0.74 [0.21 to 2.59]
	Berggren, 1987[51]	RCT/orthopedic	Epidural General	50 (14/28) 38 (11/29)	1.32 [0.73 to 2.39]
	Sieber, 2010[39]	RCT/orthopedic	Light sedation Deep sedation	19 (11/57) 40 (23/57)	0.48 [0.26 to 0.89]
	Hudetz, 2009[41]	RCT/cardiac surgery	Adjuvant Ketamine (during induction) Placebo	3 (1/29) 31 (9/29)	0.11 [0.02 to 0.82]
Postoperative Sedation	Maldonado, 2009[42]	RCT/cardiac surgery	Dexmedetomidine Propofol	10 (4/40) 44 (16/36)	0.23 (0.08 to 0.61)
	Maldonado, 2009[42]	RCT/cardiac surgery	Dexmedetomidine Midazolam	10 (4/40) 43 (17/40)	0.24 (0.09 to 0.64)
Delirium Free Protocol	Aizawa, 2002[49]	RCT/gastrointestinal	Benzodiazepines+Pethidine Usual care	5 (1/20) 35 (7/20)	0.14 (0.02 to 1.06)
Melatonin	Al-Aama, 2011[37]	RCT/internal medicine	Melatonin Placebo	11 (7/61) 31 (19/61)	0.37 (0.17 to 0.81)
Anti-Lipid Therapy	Katznelson, 2009[52]	Non-randomized/ cardiac surgery	Statin No statin	11 (73/676) 13 (49/383)	0.84 [0.60 to 1.19]

Return to Contents

Of the five studies evaluating cholinesterase inhibitors, two non-randomized trials found that using cholinesterase inhibitors was an effective strategy for decreasing the incidence of delirium. One study compared hospitalized patients who were chronic users of rivastigmine to non-users and found a decreased incidence of delirium in the chronic users (N=40, 45.5% vs. 88.9%, p=0.007).[12] The second study compared delirium incidence in elective surgery patients given physostigmine or placebo (N=113, 28.9% vs. 69.1%, p=0.0004).[54] Three randomized, controlled trials found no difference in delirium incidence between intervention and control subjects using rivastigmine in cardiac surgery patients (N=120, 32.1% vs. 29.8%, p=0.79)[40] or donepezil in hip replacement patients (N=50, 10.5% vs. 35.7%, p=0.08)[45] and hip and knee replacement patients (N=80, 20.5% vs. 17.1%, p=0.69).[47] There were no reported differences between intervention and control groups in delirium severity, delirium duration, hospital length of stay, or use of rescue medications.

Four studies looked at different anesthesia protocols. One study found that limiting the depth of intra-operative sedation during spinal anesthesia for hip fracture repair decreased the incidence of delirium in subjects receiving light sedation vs. subjects receiving deep sedation (N=114, 19% vs. 40%, p=0.02).[39] This intervention was also found to decrease delirium duration (0.5 days (SD 1.5) vs. 1.4 days (SD 4.0), p=0.01), but did not have a significant effect on delirium severity or hospital length of stay. In veterans undergoing elective cardiac surgery with cardiopulmonary bypass, ketamine (vs. saline) during anesthetic induction significantly reduced the incidence of delirium (N=58, 3.4% vs. 31.0%, p=0.01)[41] Length of stay did not differ. A small, single site study comparing regional (epidural or spinal) anesthesia to general anesthesia in patients undergoing elective orthopedic or vascular surgery found no difference in the incidence of delirium (N=47, 15.8% vs. 21.4%, p=0.63).[48] Similarly, in another small study there was no significant difference in the incidence of delirium in patients receiving epidural vs. general anesthesia during femoral neck fracture repair (N=57, 50% vs. 27.9%, p=0.36).[51]

Of the four studies evaluating antipsychotic medications, all involved surgical patients. Three found a significantly lower incidence of delirium in the intervention groups compared to the control groups[38,44,50] The studies all compared use of prophylactic antipsychotics to that of placebo; one used olanzapine perioperatively in patients undergoing total knee or hip replacement (N=495, 14.3% vs. 40.2%, p<0.0001),[38] one used risperidone following elective cardiac surgery with cardiopulmonary bypass (N=126, 11.1% vs. 31.7%, p=0.009),[44] and one use haloperidol following gastrointestinal surgery(N=80, 10.5% vs 32.5%, p<0.05).[50] A more recent study of haloperidol for patients undergoing elective hip surgery found no difference (N=430, 15.1% vs. 16.5%, p=0.69).[46] The study using olanzapine also found a decrease in delirium severity (DRS-R-98 score of 16.4 (SD 3.7) vs. 14.5 (SD 2.7), p=0.002) and duration (2.2 days (SD 1.3) vs. 1.6 (SD 0.7), p=0.02) in the treatment group;[38] these outcomes were not reported in the study using risperidone[44] or in one of the haloperidol studies[50] The second haloperidol study reported significant decreases in severity and duration of delirium (both p<0.01) and a difference in length of stay for patient who developed delirium (11.1 days vs. 16.7 days, p<0.001)[46]

Of the three studies evaluating analgesia, two studies found enhanced pain prophylaxis decreased delirium incidence. One studied used a fascia iliaca compartment block (injection of local anesthesia beneath the fascial layer of the iliopsoas muscle as an approach to reaching the nerves of the lumbar plexus) vs. placebo before and after hip fracture surgery (N=219, 10.8%

vs. 23.8%, p=0.02).[43] The other study, a retrospective comparison of patients who received patient-controlled femoral nerve analgesia vs. intravenous analgesia following hip fracture surgery (N=99, 8.2% vs. 42.0%, p<0.001).[53] A third study did not find a difference in delirium incidence between intervention subjects using continuous epidural bupivicaine and fentanyl vs. control subjects using continuous IV fentanyl for pain following bilateral knee replacement (N=51, 38.4% vs. 44.0%, p=0.69).[13] The study using the fascia iliaca compartment block[43] found significant differences in delirium severity (DRS-R-98 score of 14.3 (SD 3.6) vs. 18.6 (3.4), p<0.001) and duration (5.2 days (SD 4.3) vs. 11.0 days (SD 7.2), p<0.001) favoring the treatment intervention. The study using the patient-controlled femoral nerve analgesia[53] found a significant difference in use of opioid rescue medications favoring the intervention group (0% vs. 28%, p<0.001).

Other pharmacologic agents studied include melatonin, bendodiazipines, other post-operative sedatives, and anti-lipids. A recent study of melatonin prior to sleep in patients on the internal medicine wards found a decreased incidence of delirium compared to patients receiving placebo (N=122, 11.5% vs. 31.1%, p=0.01).[37] Post-operative sedation with dexmedetomidine compared to either propofol or midazolam following cardiac valve surgery (with cardiopulmonary bypass) resulted in a decreased incidence of delirium (N=76, dexmedetomidine 10.0%, propofol 44.4%, midazolam 42.5%, p<0.001 dexmedetomidine vs. both controls).[42] There were also no differences in delirium duration, length of stay, or use of rescue medications.[42] A study of a delirium-free protocol (diazepam, flunitrazepam, and pethidine) vs. usual care in patients who underwent resection of gastric or colorectal cancer found no difference in the incidence of delirium (N=40, 5.0% vs. 35.0%, p=0.06).[49] Length of stay also did not differ. A non-randomized study found that administration of anti-lipid therapy did not alter the development of delirium between intervention and control subjects following cardiac surgery (N=1059, 10.8% vs.12.8%, p=0.33).[52]

Pooled Comparisons (Figure 5)

We were able to pool randomized trials of antipsychotics versus placebo studies and cholinesterase inhibitors versus placebo for analysis; the other pharmacologic trials were too heterogeneous to allow for meta-analysis. In three small trials of cholinesterase inhibitor medications versus placebo (combined n = 226),[40,45,47] prophylactic cholinesterase inhibitors (donepezil and rivastigimine) did not significantly decrease the development of delirium in older hospitalized patients (RR 0.93, 95%CI 0.51-1.69, I^2=29%).

In two trials of atypical antipsychotic medication versus placebo involving 526 individuals,[38,44] prophylactic medications significantly decreased the development of delirium in older hospitalized patients (RR 0.35, 95%CI 0.25-0.50, I^2=0%).

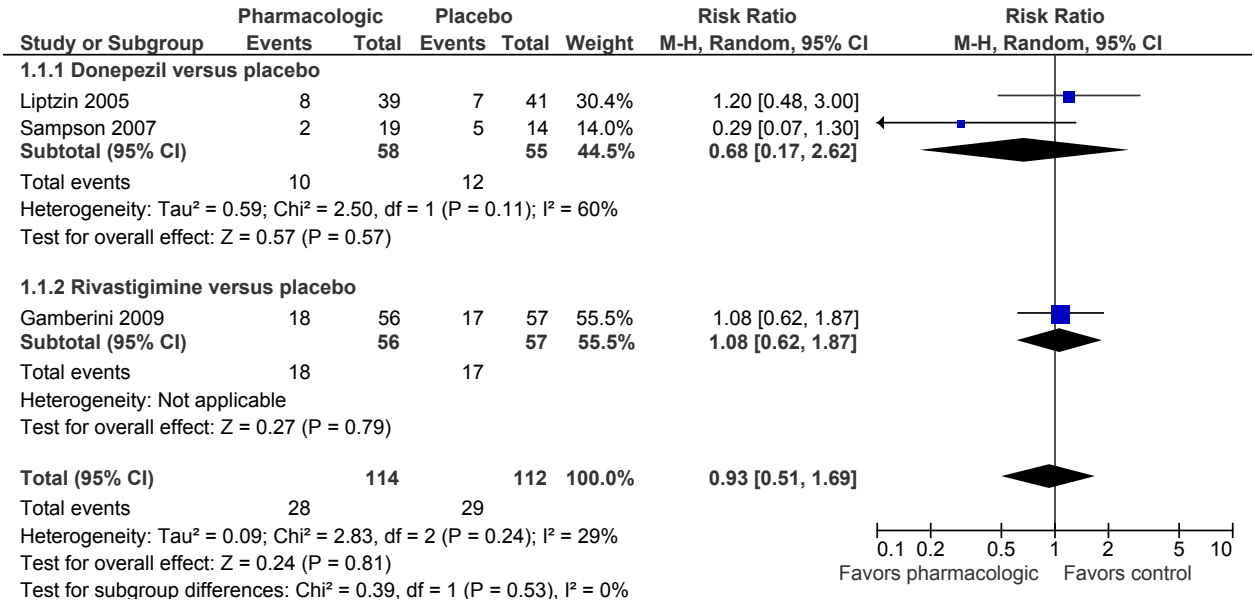
Strength of Evidence (Table 3)

We evaluated the strength of evidence for the randomized studies of pharmacologic interventions using the approach described in the Methods section. Strength of evidence was low for all of the interventions that included only one randomized trial. Study quality, reflecting risk of bias, was rated as fair for all but one of the studies. Imprecision was noted for five of the studies. With one trial, it was not possible to assess consistency of the intervention effect.

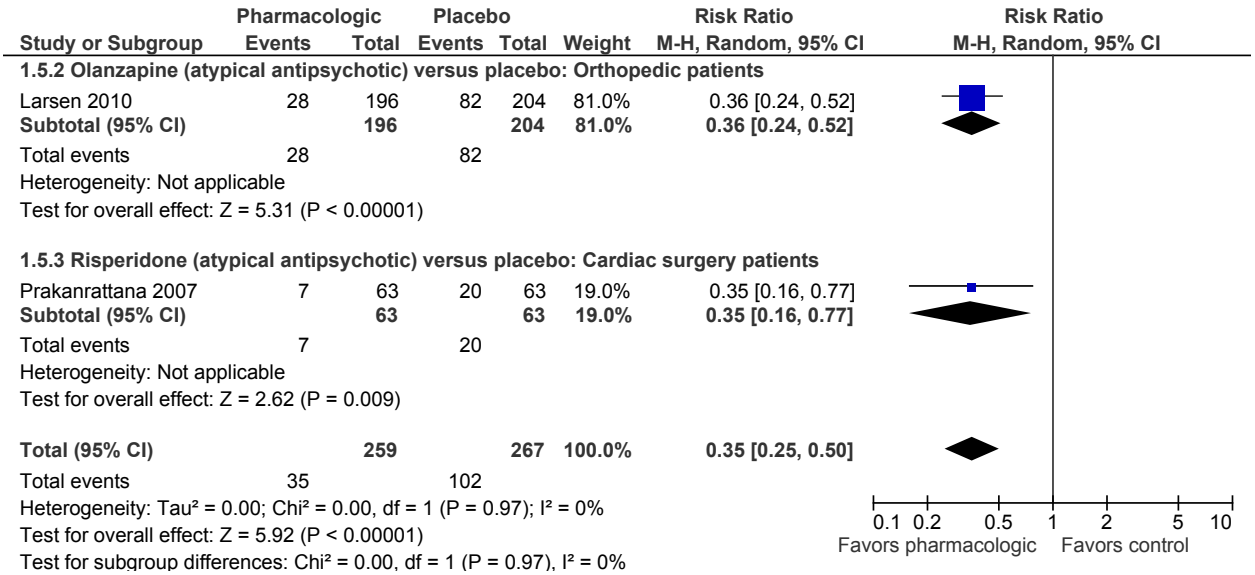
For the two comparisons with multiple trials, one was rated low (acetylcholinesterase inhibitors versus placebo) while one was rated moderate (atypical antipsychotic agents versus placebo). Overall study quality was fair for both interventions but precision and consistency were noted for the atypical antipsychotic trials.

Figure 5. Incidence of Delirium, Randomized Pharmacologic Trials

A. Acetylcholinesterase inhibitors versus placebo



B. Atypical antipsychotic agents versus placebo



Return to Contents

Table 3. Evidence Summaries for the Randomized Pharmacologic Delirium Studies: Incidence of Delirium

Intervention	Meta-analysis details; notes	Summary statistics	Quality domains	Evidence rating
Acetylcholinesterase inhibitors versus placebo Liptzin 2005; Sampson 2007; Gamberini 2009)[40,45,47]	3 trials (n=226) agents: donepezil (2) and rivastigimine	RR = 0.93 [95%CI 0.51 to 1.69]	Study quality: fair Directness: direct Imprecision: yes Inconsistency: yes	Low
Atypical antipsychotic agents versus placebo (Larsen 2010; Prakanrattana 2007)[38,44]	2 trials (n=526) agents: olanzapine and risperidone	RR = 0.32 [95%CI 0.12 to 0.91]	Study quality: fair Directness: direct Imprecision: no Inconsistency: no	Moderate
Typical antipsychotic agents versus placebo (with consultation) (Kalisvaart 2005)[46]	1 trial (n=430) proactive geriatric consultation for all patients agent: haloperidol	RR = 0.91 [95%CI 0.59 to 1.42]	Study quality: good Directness: direct Imprecision: yes Inconsistency: NA	Low
Typical antipsychotic agents versus placebo (Kaneko 1999)[50]	1 trial (n=78) agent: haloperidol	RR = 0.32 [95%CI 0.12 to 0.91]	Study quality: fair Directness: direct Imprecision: no Inconsistency: NA	Low
Fascia iliaca block versus placebo (Mouzopolous 2009)[43] *Analgesia*	1 trial (n=207)	RR = 0.45 [95%CI 0.24 to 0.87]	Study quality: fair Directness: direct Imprecision: no Inconsistency: NA	Low
Continuous epidural versus continuous intravenous (Williams-Russo 1992)[13] *Analgesia*	1 trial (n=51)	RR = 0.87 [95%CI 0.45 to 1.69]	Study quality: fair Directness: direct Imprecision: yes Inconsistency: NA	Low
Deep sedation versus light sedation (Sieber 2010)[39] *Anesthesia*	1 trial (n=114) agent: propofol	RR = 0.48 [95%CI 0.26 to 0.89]	Study quality: fair Directness: direct Imprecision: no Inconsistency: NA	Low
Ketamine bolus versus placebo (Hudetz 2009)[41] *Anesthesia*	1 trial (n=58) administered during anesthetic induction	RR = 0.11 [95%CI 0.02 to 0.82]	Study quality: fair Directness: direct Imprecision: no Inconsistency: NA	Low

Return to Contents

Intervention	Meta-analysis details; notes	Summary statistics	Quality domains	Evidence rating
Regional anesthesia versus general anesthesia (Papaioannou 2005)[48] *Anesthesia*	1 trial (n=47) regional was either epidural or spinal	RR = 0.74 [95%CI 0.21 to 2.59]	Study quality: fair Directness: direct Imprecision: yes Inconsistency: NA	Low
Epidural anesthesia versus general anesthesia (Berggren 1987)[51] *Anesthesia*	 (n=57) 	RR = 1.32 [95%CI 0.73 to 2.39]	Study quality: fair Directness: direct Imprecision: yes Inconsistency: NA	Low
Postoperative dexmedetomidine Sedation versus postoperative propofol sedation (Maldonado 2009)[42]	1 trial (n=76) 	RR = 0.23 [95%CI 0.08 to 0.61]	Study quality: fair Directness: direct Imprecision: no Inconsistency: NA	Low
Postoperative dexmedetomidine Sedation versus postoperative midazolam sedation (Maldonado 2009)[42]	1 trial (n=80) 	RR = 0.24 [95%CI 0.09 to 0.64]	Study quality: fair Directness: direct Imprecision: no Inconsistency: NA	Low
Delirium free protocol (DFP) versus usual care (Aizawa 2002)[49]	1 trial (n=40) DFP: benzodiazepines and pethidine	RR = 0.14 [95%CI 0.02 to 1.06]	Study quality: fair Directness: direct Imprecision: yes Inconsistency: NA	Low
Melatonin versus placebo (Al-Aama 2011)[37]	1 trial (n=122) 	RR = 0.37 [95%CI 0.17 to 0.81]	Study quality: fair Directness: direct Imprecision: no Inconsistency: NA	Low
The remaining nonrandomized studies (Katznelson 2009, anti-lipid therapy;[52] Del Rosario 2008, analgesia;[53] Dautzenberg 2004 and Savage 1978, both acetylcholinesterase inhibitors[12,54]) should be considered at high-risk of bias due to lower study quality and therefore the summary of evidence is low.				

CI = confidence interval; NA = not applicable; RR = relative risk

Return to Contents

Non-Pharmacologic or Mixed Studies

Nineteen studies, including 5 randomized, controlled trials and 14 non-randomized trials, evaluated non-pharmacologic or mixed methods of delirium prevention (Tables 4 and 5, Appendix D, Tables 3 and 4). Included patients tended to be at moderate-to-high risk for delirium, with patients recruited post-operatively, from ICUs or traumatological unit, or as geriatric internal medicine patients. The studies were widely variable in their interventions and reporting of outcomes. All reported on some measure of delirium incidence, 4 studies reported delirium severity, 7 studies reported delirium duration, 11 studies reported length of stay, and 2 studies reported on the use of rescue medications). Of the 5 randomized trials, one assessed music therapy, one bright light therapy, one proactive geriatrics consultation and two involved staff education and varying multi-component interventions.

Sixteen of the nineteen non-pharmacologic prevention studies examined multi-component interventions (see Table 4). Authors reported a significantly lower incidence of delirium in the intervention group in 2 of the 3 randomized trials and 10 of the 12 non-randomized trials ($p<0.05$) with one trial not reporting the significance level (Appendix D, Table 2). When relative risks were determined, all but one study found a reduced risk of delirium in the intervention; the difference was significant in 1 of the 3 randomized trials and 6 of the 12 non-randomized trials (Table 5). Relative risks in the 3 randomized trials ranged from 0.65 to 1.01; in the 12 non-randomized trials, the range was 0.16 to 0.88. Of four multi-component studies reporting delirium severity, two reported that the intervention decreased severity.[65,70] Three of seven studies reporting decreased delirium duration reported significantly better outcomes in the intervention group.[55,70,71] Of eleven studies reporting length of stay, four found significantly shorter hospitalization for intervention patients with differences of 4 to 10 days.[55,58,66,78] Both of the studies reporting on rescue medication use with found reductions among intervention patients,[55,67]

Three non-pharmacologic studies used a single intervention prevention strategy including randomized trials of bright light therapy[56] and music[57] and a non-randomized study of staff education alone.[68] Using bright lights to enhance daytime awakening was not found to be an effective prevention strategy for delirium (N=15, 16.7% vs. 40.0%, p=0.42),[56] however, playing largely instrumental, soothing music four times per day significantly decreased delirium incidence (N=126, 3.2% vs. 58.1%, p=0.001).[57] A third study found that educating staff to increase delirium awareness and knowledge was effective in decreasing delirium incidence (N=250, 9.8% vs. 19.5%, p=0.03).[68] None of these studies reported on other delirium outcomes.

Pooled Comparisons

The non-pharmacologic or mixed delirium prevention strategies could not be pooled due to the heterogeneity of the interventions tested.

Strength of Evidence (Table 6)

We determined strength of evidence for the five randomized trials of non-pharmacologic interventions. One study was rated moderate due to the higher quality (lower risk of bias) of the study; the remaining four were rated low. Due to heterogeneity of the interventions, we did not rate the strength of evidence for the non-randomized trials.

Table 4. Components of Multi-Component Interventions for Delirium Prevention

Study/Patients	Multi-Disciplinary Team	Staff Education	Patient Assessment	Orientation and/or Sensory Impairment Training	Sleep Protocol	Early Mobilization	Environmental Modification	Medication Modification/ Pain Management	Nutrition/ Hydration
Randomized Controlled Trials									
Lundstrom 2007[55]/orthopedic (other-individual care planning, bowel/bladder function, oxygen)	√	√	√		√	√		√	√
Lundstrom 2005[58]/internal medicine (items covered in nurse and staff training)		√	√	√				√	
Marcantonio 2001[59]/orthopedic (other – oxygen, bowel/bladder function)			√	√		√	√	√	√
Non-randomized Trials									
Ushida 2009[60]/neurology					√	√		√	
Vidan 2009[61]/internal medicine	√	√	√	√	√	√		√	√
Kratz 2008[62]/medical-surgical	√	√	√	√	√	√	√	√	√
Robinson 2008,[63] Vollmer 2007[64]/renal	√	√	√	√		√	√		
Caplan 2007[65]/geriatrics			√	√					√
Harari 2007[66]/orthopedic (other-bowel/bladder function, discharge planning)	√		√			√		√	√
Naughton 2005[67]/medicine	√	√	√		√	√	√	√	
Wong Tim Niam 2005[69]/orthopedic (other-bladder/bowel function, oxygen)		√	√	√		√	√	√	√
Milisen 2001[70]/traumatologic		√	√					√	
Inouye 1999[71] and 4 related publications[72-75]/ general medicine	√	√	√	√	√	√			√
Lundstrom 1999[76]/orthopedic (other-oxygen)	√	√	√			√	√		√
Wanich 1992[77]/general medicine (other-discharge planning, caregiver education)		√	√	√		√	√	√	
Gustafson 1991[78]/orthopedic (other-surgery policy, oxygen, anesthetic technique)	√		√						

Return to Contents

Table 5: Incidence of Delirium - Non-Pharmacologic or Mixed Treatments Prevention Studies

Study	Study Type/Patients	Intervention Control	Delirium Incidence/ Prevalence % (n/N)	Relative Risk [95% Confidence Interval]
Lundstrom, 2007[55]	RCT/orthopedic	Multi-factorial intervention	55 (56/102)	0.73 [0.59 to 0.90]
		Usual care	75 (73/97)	
Taguchi, 2007[56]	RCT/ICU	Bright light therapy	17 (1/6)	0.42 [0.05 to 3.36]
		Natural lighting environment	40 (2/5)	
McCaffrey, 2006[57]	RCT/orthopedic	Music plus usual care	3 (2/62)	0.06 [0.01 to 0.22]
		Usual care	58 (36/62)	
Lundstrom, 2005[58]	RCT/general medicine	Multi-component including education	32 (63/200)	1.01 [0.76 to 1.36]
		Usual care	31 (62/200)	
Marcantonio, 2001[59]	RCT/orthopedic	Proactive geriatrics consultation	32 (20/62)	0.65 [0.42 to 1.00]
		Usual care	50 (32/64)	
Ushida, 2009[60]	Non-randomized/ neurology	Modified protocol	8 (3/38)	0.28 [0.09 to 0.87]
		Usual care	28 (23/81)	
Vidan, 2009[61]	Non-randomized/ geriatric medicine	Multi-disciplinary/component intervention	12 (20/170)	0.63 [0.40 to 1.01]
		Usual care	19 (69/372)	
Robinson, 2008[63,64]	Non-randomized/ renal	Delirium protocol	14 (11/80)	0.37 [0.20 to 0.68]
		Usual care	38 (30/80)	
Caplan, 2007[65]	Non-randomized/ geriatric	Multi-component intervention	6 (1/16)	0.16 [0.02 to 1.18]
		Usual care	38 (8/21)	
Harari, 2007[66]	Non-randomized/ orthopedic	Proactive care of older people (POPS)	6 (3/54)	0.30 [0.09 to 1.03]
		Pre-POPS	19 (10/54)	
Naughton, 2005[67] *4-month cohort*	Non-randomized/ geriatric or general med	Multi-factorial intervention	23 (35/154)	0.56 [0.38 to 0.80]
		Pre-intervention strategy	41 (45/110)	
Naughton, 2005[67] *9-month cohort*	Non-randomized/ geriatric or general med	Multi-factorial intervention	19 (21/110)	0.47 [0.30 to 0.73]
		Pre-intervention strategy	41 (45/110)	
Tabet, 2005[68]	Non-randomized/ medicine	Educational package	10 (12/122)	0.50 [0.26 to 0.96]
		No educational package	20 (25/128)	
Wong Tim Niam, 2005[69]	Non-randomized/ orthopedic	Quality improvement program	13 (9/71)	0.35 [0.16 to 0.78]
		No program group	36 (10/28)	
Milisen, 2001[70]	Non-randomized/ traumatological ward	Education of nursing staff	20 (12/60)	0.86 [0.46 to 1.45]
		Usual care	23 (14/60)	
Inouye, 1999[71-75]	Non-randomized/ general medicine	Multi-component strategy	10 (42/426)	0.66 [0.46 to 0.95]
		Matched controls	15 (64/426)	
Lundstrom, 1999[76]	Non-randomized/ orthopedic	Multi-component/education	31 (15/49)	0.56 [0.36 to 0.87]
		Usual care or medical intervention	55 (117/214)	
Wanich, 1992[77]	Non-randomized/ general medicine	Multi-component/education	19 (26/135)	0.88 [0.53 to 1.45]
		Usual care	22 (22/100)	
Gustafson, 1991[78]	Non-randomized/ orthopedic	Surgical/anesthesia policy	48 (49/103)	0.78 [0.60 to 1.00]
		Pre-surgical/anesthesia policy	61 (68/111)	

RCT = randomized controlled trial

Return to Contents

Table 6. Evidence Summaries for the Randomized Non-pharmacologic Delirium Studies: Incidence of Delirium

Intervention	Meta-analysis details; notes	Summary statistics	Quality domains	Evidence rating
Multi-factorial intervention (postoperative) program versus usual care (Lundstrom 2007)[55] *Orthopedics*	1 trial (n=199) program elements included: a) multi-disciplinary team; b) staff education; c) patient assessment; d) sleep protocol; e) early mobilization; f) medication modification/pain management; g) nutrition/hydration	RR = 0.73 [0.59 to 0.90]	Study quality: good Directness: direct Imprecision: no Inconsistency: NA	Moderate
Multi-component intervention versus usual care (Lundstrom 2005)[58] *Internal medicine*	1 trial (n=400) program elements included: a) staff education; b) patient assessment; c) orientation and/or sensory impairment training; d) medication modification/ pain management	RR = 1.01 [0.76 to 1.36]	Study quality: fair Directness: direct Imprecision: no Inconsistency: NA	Low
Multi-component intervention (proactive geriatrics consultation (preoperatively or within 24 hours of surgery) versus usual care (Marcantonio 2001)[59] *Orthopedics*	1 trial (n=126) program elements included: a) patient assessment; b) orientation and/or sensory impairment training; c) early mobilization; d) environmental modification; f) nutrition/hydration	RR = 0.65 [0.42 to 1.00]	Study quality: fair Directness: direct Imprecision: yes Inconsistency: NA	Low
Bright light therapy versus Natural lighting environment (Taguchi 2007)[56] *ICU,*	1 trial (n=15) patients undergoing surgery for esophageal cancer	RR = 0.42 [0.05 to 3.36]	Study quality: fair-poor Directness: direct Imprecision: yes Inconsistency: NA	Low
Usual post-operative care plus music versus usual post-operative care (McCaffrey 2006)[57] *Orthopedics*	1 trial (n=126) patient's choice from CDs provided	RR = 0.06 [0.01 to 0.22]	Study quality: fair-poor Directness: direct Imprecision: no Inconsistency: NA	Low
The remaining nonrandomized studies should be considered at high-risk of bias due to lower study quality and therefore the summary of evidence is low.				

CI = confidence interval; ICU = intensive care unit; NA = not applicable; RR = relative risk

Harms

Mortality and adverse event data are reported on Table 7. Only trials reporting adverse event or mortality data are listed. Due to incomplete reporting and widely varying level of detail among studies that did report, it is difficult to determine whether one type of intervention was more likely to result in adverse events or deaths.

Mortality

Seven studies of pharmacological interventions and eleven studies of non-pharmacological interventions report mortality data. Only one study, using a multi-component intervention, reported a difference in mortality between intervention and control groups. For patients who developed delirium, a lower mortality rate was found in the intervention group versus the control group (2 deaths in 63 intervention subjects ([3.2%] versus 9 deaths in 62 control subjects [14.5%], p=0.03).[58]

Adverse Events

Reporting of adverse events varied. Thirteen of twenty pharmacologic intervention studies and seven of nineteen non-pharmacologic intervention studies reported adverse event data. Overall, few differences between intervention and control groups were found. Among studies of pharmacologic interventions, the only significant adverse event related to use of restraints. One study of patients admitted to internal medicine units from the emergency department found that fewer patients treated with melatonin required restraints (6.6% vs. 9.8%, p=0.03).[37] A second study, with patients who underwent elective total knee or total hip replacement surgery and received either olanzapine or placebo, found increased use of restraints in the intervention group (2.6% vs. 0%, p=0.03).[38]

Among studies of non-pharmacologic interventions, four studies reported significant differences in adverse events. One study, comparing a multi-factorial intervention to usual care in orthopedic patients, found fewer bed sores (9% vs. 22%) urinary tract infections (31% vs. 51%), nutritional complications (25% vs. 38%), and falls (12% vs. 27%) in the intervention group (all p<05).[55] A second study, before and after implementation of a multidisciplinary program for patients undergoing elective orthopedic surgery, reported decreased uncontrolled pain (2% vs. 30%) and pressure sores (4% vs. 19%), and fewer patients with bedridden status (9% s. 28%) or unable to perform independent transfers on the third post-operative day (0% vs. 15%) (all p<0.05).[66] Another pre-post study found fewer pressure sores (4% vs. 13%) and fewer severe falls (0% vs. 5%) (both p<0.05) in patients undergoing surgery for hip fractures.[78]. Finally, implementation of a multi-component protocol in the medical-surgical unit was associated with a "statistically significant" reduction in restraint use.[62]

Table 7. Adverse Events and Mortality – Prevention Studies

Author, Year	Adverse Events n/N (%)		Mortality n/N (%)	
	Intervention	Control	Intervention	Control
Pharmacologic Treatments				
Randomized trials				
Al-Aama 2011[37]	Two patients on melatonin reported side effects that might have been secondary to the study medication or related to delirium directly (1 patient reported nightmares and 1 patient reported feeling like he was "floating around and talking to his dead wife") *Clinical interventions* Restraints 4/61 (6.6), p=0.03 Use of paid attendant services 2/57 (4 missing) (3.5)	*Clinical interventions* Restraints 6/61 (9.8) Use of paid attendant services 1/60 (1 missing) (1.7)	6/61 (9.8), p=0.78 Plus additional deaths from patients excluded from study analyses (n not reported)	8/61 (13.1) Plus additional deaths from patients excluded from study analyses (n not reported)
Larsen 2010[38]	Atrial fibrillation 6/196 (3.1), p=NS Arrhythmia 2/196 (1.0), p=NS Congestive heart failure 1/196 (0.5), p=NS Alcohol withdrawal 5/196 (1.0), p=NS Pneumonia 3/196 (1.5), p=NS Urinary tract infection 1/196 (0.5%), p=NS *Clinical interventions* Sitter 9/196 (4.6), p=NS Restraints 5/196 (2.6), p=0.03 Bed alarm 11/196 (5.6), p=NS	Atrial fibrillation 3/204 (1.5) Arrhythmia 1/204 (0.5) Congestive heart failure 1 /204 (0.5) Alcohol withdrawal 1 /204 (0.5) Pneumonia 0/204(0) Urinary tract infection 4/204 (2.0) *Clinical interventions* Sitter 4/204 (2.0) Restraints 0/204 Bed alarm 7/204 (3.4)		
Sieber 2010[39]	Deep sedation Patients ≥ 1 complication 30/57 (52.6), p=0.57 Patients with postoperative complications (averaged over the entire population of each group include the following: urinary tract infection, discharge with urinary drainage catheter, acute renal failure, pneumonia, congestive heart failure, myocardial infarction, new dysrhythmia, fall, return to surgery, pulmonary embolus or deep venous thrombosis, or wound infection) 1.0 (1.8), p=NS	Light sedation Patients ≥ 1 complication 26/57 (45.6) Patients with postoperative complications (averaged over the entire population of each group) 0.8 (1.4)	Deep sedation Intraoperative 0/57, p>0.99 During hospitalization 2/57 (3.5), p>0.99	Light sedation Intraoperative 0/57 During hospitalization 1/57 (1.8)

Return to Contents

Author, Year	Adverse Events n/N (%)		Mortality n/N (%)	
	Intervention	Control	Intervention	Control
Gamberini 2009[40]	Perioperative stroke 1/59 (1.7), p=1.0 Seizures 0/59, p=1.0 Nausea 40/59 (67.8), p=0.1 Vomiting 27/59 (45.8), p=0.6 Anorexia 39/59 (66.1), p=1.0 Diarrhea 7/59 (11.9), p=0.8 Vertigo 28/59 (47.5), p=0.5 Insomnia 33/59 (55.9), p=0.1 Atrial fibrillation 22/59 (37.3), p=0.6 Life-threatening arrhythmia 3/59 (5.1), p=1.0 Pacemaker >1 day 15/59 (25.4), p=0.12	Perioperative stroke 2/61 (3.3) Seizures 1/61 (1.6) Nausea 32/61 (52.5) Vomiting 24/61 (39.3) Anorexia 41/61 (67.2) Diarrhea 6/61 (9.8) Vertigo 24/61 (39.3) Insomnia 24/61 (39.3) Atrial fibrillation 26/61 (42.6) Life-threatening arrhythmia 3/61 (4.9) Pacemaker >1 day 24/61 (39.3)	1/59 (1.7), p=1.0	1/61 (1.6)
Maldonado 2009[42]	Postoperative hypotension 2/40 (5.0)	Midazolam group Inoperative CVA 1/40 (2.5)	0/40 Dexmedetomidine	2/38 (5.3) Propofol 0/40 Midazolam
Mouzopolous 2009[43]	3 local hematomas developed at the injection site which “resolved spontaneously”, p=NR		1/108 (0.9), p=NR	2/111 (1.8)
Sampson 2007[45]	Nausea 6/19 (31.6), p=0.5 Vomiting 3/19 (15.8), p=0.5 Diarrhea 3/19 (15.8), p=0.9 Insomnia 9/19 (47.4), p=0.2 Dizziness 4/19 (21.1), p=0.3 Paresthesia 1/19 (5.3), p=0.8 Fever 1/19 (5.3), p=0.8 Subjects with 1 AE 1/19 (5.3), p=0.4 Subjects with 2 AE 17/19 (89.5), p=0.4	Nausea 6/14 (42.9) Vomiting 1/14 (7.1) Diarrhea 2/19 (10.5) Insomnia 10/19 (52.6) Dizziness 1/14 (7.1) Paresthesia 1/14 (7.1) Fever 1/14 (7.1) Subjects with 1 AE 2/14 (14.3) Subjects with 2 AE 11/14 (78.6)		
Kalisvaart 2005[46]	3 subjects withdrew due to adverse events No drug-related side effects were observed during study period.	3 subjects withdrew due to adverse events		
Papaioannou 2005[48]	Postoperative complications 5/19 (26.3), p=NS	Postoperative complications 8/28 (28.6)		
Aizawa 2002[49]	Surgical complications 5/20 (25.0) Morning lethargy 8/20 (40.0)	Surgical complications 5/20 (25.0)		
Williams-Russo 1992[13]	Complications not reported by treatment arm. Thrombocytopenia 20/51 (39.2) Atrial arrhythmias 11/51 (21.6) Hyponatremia 11/51 (21.6) Urinary tract infections 3/51 (5.9)			

Return to Contents

Author, Year	Adverse Events n/N (%)		Mortality n/N (%)	
	Intervention	Control	Intervention	Control
Berggren 1987[51]	Pneumonia 1/28 (3.6) Pulmonary embolism 2/28 (7.1) Cardiac failure 2/28 (7.1) Depression 3/28 (10.7) Urinary incontinence 6/28 (21.4) Urinary retention 5/28 (17.9) Urinary tract infection 9/28 (32.1) Urosepsis 1/28 (3.6) Decubitus ulcer 3/28 (10.7) Stroke 3/28 (10.7) All comparisons p=NS	Pneumonia 2/29 (6.9) Depression 3/29 (10.3) Urinary incontinence 5/29 (17.2) Urinary retention 6/29 (20.7) Urinary tract infection 7/29 (24.1) Decubitus ulcer 5/29 (17.2)	One death on the first postoperative day. *3 additional deaths (group not defined) within 5 months post surgery*	*See intervention*
Non-randomized trials				
Del Rosario 2008[53]	No statistically significant differences (p>0.05) in the transfusion index, hemoglobin level and rate of medical postoperative complications.			
Dautzenberg 2004[12]			0/11, p>0.05	0/29
Savage 1987[54]				
Non-Pharmacologic Studies				
Randomized trials				
Lundstrom 2007[55]	During hospitalization (significant differences vs. control*) Bedsores 9/102 (8.8), p=0.01 Urinary tract infection 32/102 (31.4), p=0.01 Nutritional complications 25/102 (24.5), p=0.04 Falls 12/102 (11.8), p=0.01	During hospitalization Bedsores 21/95 (22.1) Urinary tract infection 49/96 (51.0) Nutritional complications 37/97 (38.1) Falls 26/97 (26.8)	Over 12-month follow-up: 16/102 (15.7), p=NS	Over 12-month follow-up: 18/97 (18.6)
Taguchi 2007[56]	A few patients had to be reintubated (numbers not provided)			
Lundstrom 2005[58]			Delirium patients 2/63 (3.2) p=0.03	Delirium patients 9/62 (14.5)
Non-randomized trials				
Vidan 2009[61]			10/170 (5.8) Delirium patients 2/20 (10.0), p=0.60	19/372 (5.1) Delirium patients 10/69 (14.5)
Kratz 2008[62]	After implementation of acute confusion (AC) protocol Fall rate per 1000 patient days: 3.6 (in 2005); 3.6 (in 2006); 4.2 (in 2007), p=NR Restraint episodes per 1000 patient days: 1.3 (in 2005); 1.4 (in 2006); 0.09 (in 2007), reported to be ”statistically significant”	Prior to implementation of AC protocol (2004) Fall rate per 1000 patient days: 4.8 Restraint episodes per 1000 patient days: 8.7		

Return to Contents

Author, Year	Adverse Events n/N (%)		Mortality n/N (%)	
	Intervention	Control	Intervention	Control
Caplan 2007[65]			0/16, p=NR	1/21 (4.8)
Harari 2007[66]	Uncontrolled pain: 1/54 (1.9), p<0.01 No food for ≥ 4 days post-op: 0/54 Pressure sores: 2/54 (3.7), p=0.03 Bedridden: 5/54 (9.3), p=0.01 Dependent transfers on day 3 post-op: 0/54, p<0.01	Uncontrolled pain: 16/54 (29.6) No food for ≥ 4 days: 5/54 (9.3) Pressure sores: 10/54 (18.5) Bedridden: 15/54 (27.8) Dependent transfers on day 3 post-op: 8/54 (14.8)	0/54, p=NR	1/54 (1.9)
Wong Tim Niam 2005[69]			Baseline period 2/28 (7.1), p=NR	Post-intervention 3/71 (4.2)
Milisen 2001[70]			Small number of deaths in the sample OR for death in intervention cohort vs. non-intervention cohort: 3.86 (95%CI 0.09-1.71)	
Inouye 1999[71]			6/426 (1.4) p=0.78	7/426 (1.6)
Lundstrom 1999[76]	Severe falls 0/49 p=0.10 vs. C1 Eating problems 1/49 (2.0) p=0.19 vs. C1	Severe falls Control 1 6/111 (5.4) Control 2 0/103 Eating problems Control 1 8/111 (7.2) Control 2 5/103 (4.9)	In-hospital 1/49 (2.0) p=0.81vs. C1, p=0.30 vs. C2 6-month 8/49 (16.3) p=0.99 vs. C1, p=0.54 vs. C2	In-hospital Control 1 3/111 (2.7) Control 2 6/103 (5.8) 6-month Control 1 18/111 (16.2) Control 2 13/103 (12.6)
Wanich 1992[77]	Complications: 25/135 (19.0), p=NS (at least 1 of 11 pre-defined events that developed in-hospital)	Complications: 16/100 (16.0)	Hospital mortality: 11/135 (8), p=NS	Hospital mortality: 5/100 (5)
Gustafson 1991[78]	Urinary infection: 33/103 (32.0), NS Decubital ulcers: 4/103 (3.9), p<0.05 Feeding problems: 5/103 (4.9), NS Severe falls: 0/103, p<0.05	Urinary infection: 26/111 (23.4) Decubital ulcers: 14/111 (12.6) Feeding problems: 8/111 (7.2) Severe falls: 6/111 (5.4)	Mortality rate was same in control and intervention studies	

NS=study reported finding was not significant but did not report p value; NR=not reported; AE=adverse event; CVA=cerebrovascular accident

*Other adverse events reported were anemia, constipation, depression, diarrhea, heart failure, pneumonia, other infections, myocardial infarction, pulmonary embolism, stroke, stomach ulcers, and urinary retention, and the occurrence of these was not significantly difference between intervention and control groups.

Return to Contents

QUESTION 2a: Do these results vary by medical unit, age, gender, or comorbid conditions?

None of the included studies were stratified by medical unit, age, or comorbid conditions. Likewise, none of the studies were stratified by gender, although two studies included only men.[41,56] Therefore, we are unable to ascertain whether effectiveness varied by medical unit, age, gender or comorbid conditions.

Conclusions

Most of the included studies enrolled patients at high or very high risk of delirium as evidenced by incidence rates of delirium in the control group of 29-60%. The applicability of these findings to settings and patients with lower delirium risk is not clear. Low level evidence suggests that certain pharmacologic strategies in selected surgical settings may be useful. These include perioperative analgesia via fascia iliaca compartmental block for patients undergoing surgery for hip fracture, atypical antipsychotics, and lighter anesthesia. However, studies examining each category of prevention medications were small in size and number and inconsistencies in outcomes for various interventions occurred that are difficult to explain by patient population or setting (e.g. haloperidol was beneficial in patients undergoing gastrointestinal but not orthopedic surgery). Thus some findings could be due to chance or true effects could be missed due to small sample size and low event rates. There is low level evidence that use of cholinesterase inhibitors or perioperative statins do not reduce the risk of delirium. There is mixed evidence for continuous epidural bupivicaine plus fentanyl versus continuous IV fentanyl.

Multi-component strategies were generally successful in delirium prevention, although the interventions studied varied widely and often involved several strategies and disciplines. Thus it is difficult to determine the specific component(s) of effectiveness. Evidence suggests that staff education alone may be an effective strategy, as may be music therapy, although there are currently only two studies supporting these strategies. There is no evidence of a difference in delirium incidence associated with bright light therapy. Overall, the evidence suggests that there are few harms associated with the methods used in these studies for delirium prevention. However, it is difficult to determine the true extent of harms and whether they differ between pharmacologic and non-pharmacologic interventions due to incomplete reporting. None of the included studies were stratified by medical unit, age or comorbid conditions. Therefore, there are no data addressing whether the effectiveness or harms varies by medical unit, age, gender or comorbid conditions.

KEY QUESTION #3. What is the comparative diagnostic accuracy of the tools used to detect delirium:

a. In elderly medical and surgical inpatients?

b. In elderly ICU inpatients?

Elderly Medical and Surgical Inpatients

A recent systematic review addressed the accuracy of tools used to diagnose the presence of delirium in adults.[79] We assessed the relevance of this review as recommended in the Agency for Healthcare Research and Quality Methods Guide.[80] We found the review to be relevant - addressing the population, intervention, comparators, outcomes, timing, setting of interest for our review and including appropriate study designs. The exception was the exclusion of studies of delirium assessment for patients in an intensive care unit (ICU). We present those studies in Key Question 3b. We determined that the quality of the existing review was "good" based on the AMSTAR guidelines[81]

The review included citations from MEDLINE (1950 to May 2010), EMBASE (1980 to May 2010), and a hand-search of bibliographies of relevant articles. The review was limited to studies that included hospitalized patients (not in the ICU), used an appropriate reference standard (especially DSM-III, DSM-III-R, or DSM-IV) performed by a specialist physician, applied the same index test to more than 80% of the patients, and included patients with and without delirium. Studies that enrolled primarily children or patients with alcohol-related delirium were excluded as were studies where the same individual performed both the index and reference tests. Study quality was assessed using the method described in the Rationale Clinical Examination series as described in the Methods section.[8]

The review included 25 studies enrolling between 26 and 791 patients.[82-106] Although the review was not limited to studies of elderly patients, 15 of the 25 studies enrolled either patients older than 60 years or patients from geriatric units. In the 25 studies, 11 different diagnostic tools were used. The quality of 1 study was rated Level 1,[97] 7 were rated Level 2,[82,85,94,96,98-100] 9 were rated Level 3,[83,84,86,89,90,91,93,95,101] and 8 were rated Level 4.[87,88,92,95,103-106]

In nine studies that consecutively enrolled patients the prevalence of delirium ranged from 9% to 63%,[82,85,88,92,94,96,97,99,106] however only one study, which enrolled cancer patients consecutively referred for neurological or psychiatric consultation for mental status change, reported prevalence above 50%.[97] Five of the nine studies enrolled patients older than age 60 or from geriatric units.[82,85,88,92,96] Delirium prevalence in those studies ranged from 9% to 49%.

The most widely studied tool was the Confusion Assessment Method (CAM) with data reported from 12 studies that enrolled a total of 1036 patients[82-88,98-100,102]. CAM was developed to be administered by nonpsychiatric clinicians, is based on the 4 cardinal features of delirium, and takes approximately 5 minutes to administer.[84] There were no studies with Level of Evidence 1, 5 with Level of Evidence 2, 5 with Level of Evidence 3, and 2 with Level of Evidence 4. Sensitivity ranged from 13% to 98% with all but 2 studies greater than 75%. Specificity ranged from 77 to 100%. The pooled sensitivity was 86% and the pooled specificity was 93%. Positive test results were associated with a likelihood ratio that ranged from 4.1 to 167. The pooled likelihood ratio for a positive test was 9.6 (95%CI 5.8 to 16.0). Negative test results were

associated with a likelihood ratio that ranged from 0.03 to 0.85. The pooled likelihood ratio for a negative test was 0.16 (95%CI 0.09 to 0.29). There was considerable heterogeneity in the 12 studies as reflected in I^2 values of 65% for a positive test and 85% for a negative test. In 7 studies that enrolled either patients whose age was greater than 60 years or who were identified from geriatric units, sensitivity ranged from 46% to 95% and specificity ranged from 77% to 99%. Positive likelihood ratios ranged from 4.1 to 167; negative likelihood ratios ranged from 0.05 to 0.59.

Four studies evaluated the Delirium Rating Scale (DRS), a 10-item observational scale developed to be used by clinicians with psychiatric training, and based on characteristic symptoms of delirium.[91-93,97] The studies used a value of 10 or greater (on a scale of 0 to 32) to reflect a positive test. Total enrollment in these studies was 943. The pooled sensitivity was 95% and the pooled specificity was 79%. The pooled positive and negative likelihood ratios were 4.3 (95%CI 2.1 to 9.1) and 0.07 (95%CI 0.03 to 0.37), respectively. Heterogeneity associated with the likelihood ratios was low (I^2 values of 14% and 0%, respectively). Three of the studies enrolled patients from geriatric units. Two studies used a revised version of the DRS, the DRS-R-98 (total enrollment of 129). A positive test in these studies was indicated by a score greater than 20. One of the two studies enrolled patients 65 years and older. The pooled sensitivity was 93%; pooled specificity was 89%. The positive likelihood ratio was 8.0 (95%CI 2.6 to 25, $I^2 = 73\%$) and the negative likelihood ratio was 0.08 (95%CI 0.3 to 0.24, $I^2 = 0\%$).

The Memorial Delirium Assessment Scale (MDAS), a 10-item clinician evaluation based on DSM criteria and requiring approximately 10 minutes to complete, was evaluated in 3 studies (a total of 330 patients).[95,101,106] One of the studies enrolled patients from a geriatric unit. A score of 10 or greater indicated a positive test. Pooled sensitivity and specificity were both 92%. The pooled positive likelihood ratio was 12 (95%CI 2.4 to 5.8, $I^2 = 85\%$) and the pooled negative likelihood ratio was 0.9 (95%CI 0.3 to 0.38, $I^2 = 69\%$).

Two studies reported results from assessment of the 13 item Delirium Observation Screening Scale (DOSS), a tool designed for nurses and intended to identify early symptoms of delirium as part of regular care.[89,90] The total enrollment was 178; all patients were 70 years and older. Pooled sensitivity was 92%; pooled specificity was 82%. The positive likelihood ratio was 5.2 (95%CI 2.7 to 9.9, $I^2 = 65\%$); the negative likelihood ratio was 0.10 (95%CI 0.03 to 0.37; $I^2 = 0\%$).

Other tools identified in the review included the Clinical Assessment of Confusion (CAC), the Digit Span Test, the Global Attentiveness Rating (GAR), the Mini-Mental State Examination (MMSE), the Nursing Delirium Screening Scale (Nu-DESC), and the Vigilance "A" Test. Data were only reported from one study for each of these tools.

The study authors identified other factors that might influence the choice of a diagnostic test. A tool that can be completed in 5 minutes or less or completed by someone other than a specialist physician might be required in certain conditions.

Apart from studies examining the DRS, heterogeneity, as indicated by the I^2 values, was high. The authors explored the sources of heterogeneity in the studies that used the CAM. The I^2 associated with the negative likelihood ratio decreased from 85% to 0% when the analysis only

included studies where the index text was performed by a physician. The negative likelihood ratio increased only slightly (from 0.16 to 0.19). The positive likelihood ratio increased from 9.6 to 19 but the I^2 also increased slightly (from 65% to 67%). The I^2 associated with the negative likelihood ratio also decreased to 0% when only the higher quality studies (all Level of Evidence 2) were used but the likelihood ratio again increased only slightly (from 0.16 to 0.20). The effects on the positive likelihood ratio and associated I^2 value were not reported. The authors had speculated that the version of the DSM criteria used in the study might have contributed to heterogeneity but subgroup analyses based on DSM criteria did not produce different results.

Only one of the studies included in the systematic review enrolled patients from a VA medical center[82] The focus of the study was on medical-surgical inpatients, older than age 60, who were referred to a psychiatric consultation service (PCS) for evaluation or treatment of depressive symptoms. The investigator used the CAM to assess the referred patients for delirium. A PCS psychiatrist interviewed the patients and diagnosed delirium based on DSM-III-R criteria. Only patients with concordant diagnoses by the investigator and the psychiatrist were included in the analysis (n=67). Five patients were excluded because the diagnoses were not concordant. In two cases, the psychiatrist diagnosed delirium but the investigator did not. In three cases, the investigator diagnosed delirium but the psychiatrist did not. Of the 67 patients, 28 (41.8%) were diagnosed with delirium. Twenty-four of the referrals had neither delirium nor a depressive disorder. The referring providers for 23 of the 28 delirium cases were contacted. It was determined that only 3 of the providers considered delirium in the differential diagnosis.

The authors concluded that administration of the GAR, MDAS, CAM, DRS-R-98, CAC, and DOSS all produced positive results suggestive of delirium with likelihood ratios of greater than 5.0. Similarly, normal test results that decreased the likelihood of delirium with a likelihood ratio of less than 0.2 were found in studies that used the GAR, MDAS, CAM, DRS-R-98, DRS, DOSS, Nu-DESC, and the MMSE. As noted above, some of the tools were only evaluated in one study and some studies did not focus on an elderly population. Overall, the authors recommended the use of the CAM for a time-efficient, bedside delirium assessment.

One eligible study was identified in our search of the literature published after the search dates specified in the systematic review.[107] The Level of Evidence for this study is 3. Patients (n=116) admitted to the surgical, orthopedic, or gynecological ward of one hospital were evaluated. Only elective surgery cases were included. They excluded patients who were undergoing neurosurgical procedures, or who had a history of psychiatric or neurological illness, a previous cerebral insult, or a history of drug or alcohol abuse. They also excluded patients who were unable to communicate due to severe hearing loss or brain injury. Daily delirium assessments (from preoperative day to sixth day postoperative) were performed by trained research assistants supervised by a psychiatrist. All patients were tested independently with the CAM, the Nu-DESC, and the Delirium Detection Score (DDS). Diagnosis of delirium according to DSM-IV criteria was the reference.

Of the 116 patients screened, complete data were available for 88. Although patients of any age were eligible for the study, the mean age of those with complete data was 65.5 years; 64.8% were male. Delirium was diagnosed (DSM-IV criteria) in 17 (19%). Incidence of delirium based on the other assessment tools was as follows: CAM 17%, Nu-DESC 32%, and DDS 45%. The

analysis of sensitivity and specificity was based on patient days. There were a total of 512 patient days and 40 (8%) were identified as delirium according to DSM-IV criteria. With a cut-off point of 1 (greater than 1 indicating delirium), the sensitivity of the DDS was 71.2% (correct classification of 30 of the 40 patient days) and the sensitivity of the Nu-DESC was 97.7% (correct classification of 38 of 40 patient days). The overall sensitivity of the CAM was 74.9% (correct classification of 28 of 40 patient days). The CAM was the most specific (100%), followed by the Nu-DESC (92.3%), and the DDS (87.1%). The positive likelihood ratios for the CAM, Nu-DESC, and DDS were all greater than 5 while the negative likelihood ratios were all 0.33 or less.

Elderly ICU Inpatients

Instruments to detect delirium in critically ill patients, including those in the ICU, are a more recent development.[108] We identified fifteen studies, enrolling between 22 and 178 subjects, that met inclusion criteria, reporting the diagnostic accuracy of a screening/assessment tool for detection of delirium in the ICU.[109-123] Details of the studies are reported in Appendix D, Table 5.

Description of Studies

Patient Characteristics

Sample sizes ranged from 15 to 178. None of the studies reported specifically enrolling veterans. All fifteen studies reported gender, with men comprising the majority of the subjects (36 to 80%). For the thirteen studies reporting age,[109-116,118-122] the mean age ranged from 55 to 78 years. Five studies reported racial or ethnic characteristics.[109-111,115,116] Overall, the majority of the subjects in these six studies were Caucasian (50% to 88%). Six of the studies included only medical patients, six included both medical and surgical patients, one included only surgical patients, and one included only patients undergoing psychiatric care. Four of the studies included patients who were intubated;[110,112,113,118] the remainder of the studies included only patients who were not intubated. Five studies reported average ICU length of stay with values ranging from 6.0 to 9.2 days.[111,116,117,120,121]

Quality Assessment

Study quality was assessed using the method described in the Rationale Clinical Examination series as described in the Methods section.[8] Three studies were rated Level of Evidence 1,[112,113,122] four were Level 2,[114-116,123] two were Level 3,[110,111] one was Level 4,[109] and five were Level 5.[117-121]

Index and Reference Tools

In the 15 studies that met criteria, several different tools were used to identify the presence of delirium; some studies used more than one tool as the index test. The index tools studied included Confusion Assessment Method-Intensive Care Unit (CAM-ICU),[110,112,113,115,116,122] Intensive Care Delirium Screening Checklist (ICDSC),[114,117,122] Neelon and Champagne Confusion Scale (NEECHAM),[120] Delirium Detection Score (DDS),[112] CAM-ICU Flow sheet,[123] Cognitive Test for Delirium (CTD),[109] Nursing Delirium Screening Scale (Nu-DESC),[112] Memorial Delirium Assessment Scale (MDAS),[118] chart-based delirium method,[111] clinical judgment,[122] and observation checklist.[119] The index test was administered by physicians, ICU nurses, nurse researchers, trained researchers, or psychology technicians.

The reference (or "gold standard") diagnosis was determined by a psychiatrist using DSM III-R or DSM IV criteria in seven studies.[109,110,112,113,116,122,123] Another study used the DSM III-R criteria but did not report who did the assessment[119] and one study reported that the reference assessment was completed by a board certified psychiatrist but did not indicate which tool was used.[114] One study used the International Classification of Disease system (ICD-10), with the assessment by a psychiatrist, to define delirium.[118] In one study, the CAM, administered by a trained clinician researcher, was the reference test[115] while in three studies, the CAM-ICU, administered by a research nurse, was used to determine the reference diagnosis.[111.120.121] One study was a comparison of level of agreement between the ICDSC and the CAM ICU.[117]

Sensitivity and Specificity (Table 8)

The incidence of ICU delirium in the 13 studies that reported incidence ranged from 13% to 87%. It should be noted that some studies did not enroll patients consecutively. For studies using the CAM ICU and reporting sensitivity and specificity data,[110,112,113,115,116,122] sensitivity ranged from 64% to 100% and specificity ranged from 88% to 100%. One study developed a CAM-ICU Flowsheet.[123] Sensitivity and specificity averaged 90% and 100%, respectively, for two different evaluators. Sensitivity and specificity were also reported for the ICDSC (2 studies) and the Nu-DESC, DDS, CTC, MDAS, and NEECHAM (1 study each).

Other Outcomes (Table 8)

Several studies reported outcome data for patients with and without delirium. Mortality was higher for patients with delirium.[112,13,121] In one study, patients with delirium were less likely to be discharged to their home.[112] Length of stay in the ICU was higher for patients with delirium.[121,121]

Conclusions

A systematic review of bedside instruments concluded that the CAM was a suitable tool for medical and surgical inpatients, including patients in geriatric units. The conclusion was based on sensitivity, specificity, likelihood ratios and feasibility of administration. Training on use of the CAM is recommended and the tool was designed to be used during a formal cognitive assessment. Fewer studies have evaluated the diagnostic accuracy of tools to detect delirium for elderly ICU inpatients. The CAM-ICU, a version of the CAM adapted for use in the ICU, appears to have high specificity but sensitivity varies (ranging from 64 to 100%) indicating that some patients with delirium will not be identified using the CAM-ICU alone. Not all of these studies were restricted to elderly patients and most excluded patients with neurological disease or cognitive dysfunction. Other tools have been evaluated in only one or two studies.

Table 8. Outcomes – Intensive Care Unit Diagnostic Accuracy Studies

Author, Year Screening Tool	Delirium Incidence n/N (%)	Sensitivity (%)	Specificity (%)	Other Outcomes
Bergeron, 2001[114] ICDSC with cut-off score of 4	15 of 93 (16%) consecutive patients	99	64	
Ely, 2001[110] CAM-ICU	33 of 38 enrolled (87%)	Nurse 1: 95 Nurse 2: 96 Intensivist: 100	Nurse 1: 93 Nurse 2: 93 Intensivist: 89	Likelihood Ratio (+): Nurse 1: 14; Nurse 2: 14; Intensivist: 9 Accuracy 95%, 95%, 96%
Ely, 2001[116] CAM ICU	80 of 96 (83%) consecutive patients	Nurse 1: 100 Nurse 2: 93	Nurse 1: 98 Nurse 2: 100	Likelihood ratios: Nurse 1 50, Nurse 2 >100 LOS 17.9 days (mean) ICU LOS 8.3 days (mean) In hospital mortality 30.2%
Guenther, 2010[123] CAM-ICU Flowsheet	25 of 54 enrolled (46%)	Intensivist: 88 Medical Student: 92	Intensivist: 100 Medical Student: 100	
Hart, 1996[109] CTD with cut-off score <19	Not applicable	100	95	
Koolhoven, 1996[119] Observational checklist	2 of 15 enrolled (13%)	NR	NR	The 2 patients with delirium had scores >10 on DRS; 2 other patients had DRS scores >10 but symptoms did not persist so not diagnosed
Lin, 2004[113] CAM-ICU	22/102 (22%) consecutive patients	Assessor 1:91 Assessor 2: 98	Assessor 1: 95 Assessor 2: 98	Likelihood Ratio: 45.5 (Assessor 1,), 47.5 (Assessor 2) Mortality: 33% in no delirium group, 64% in delirium group
Luetz, 2010[112] CAM-ICU Nu-DESC DDS	63/156 (40%) consecutive patients	CAM-ICU: 81 Nu-DESC: 83 DDS: 30 (1st day)	CAM-ICU: 96 Nu-DESC: 81 DDS: 91 (1st day)	Mortality: 4% in no-delirium group, 24% in delirium group Discharge to home 55% in no-delirium group, 24% in delirium group
McNicoll, 2005[115] CAM ICU	11 of 22 (50%) consecutive patients	73	100	
Pisani, 2006[111] Chart-based delirium detection method	143 of 178 enrolled (80%)	64	85	All patients: ICU LOS: 8.2 days (mean); 5.0 days (median)
Plaschke, 2008[117] CAM-ICU and ICDSC	71 of 174 enrolled (41%)	N/A	N/A	Kappa coefficient .80 (CI 95%: 0.76-0.85) ICU LOS: 9.2 days (mean) Hospital LOS: 24.0 days (mean) In-hospital mortality: 19%
Shyamsundar, 2009[118] MDAS with cut-off score of 10 (unclear how many patients were assessed with reference test)	NR	100	96	

Author, Year Screening Tool	Delirium Incidence n/N (%)	Sensitivity (%)	Specificity (%)	Other Outcomes
Spronk, 2009[121] Clinical judgment	23 of 46 enrolled (50%)	Physicians: 28 Nurses 35 (for days with delirium)	Physicians: 100 Nurses: 98.3 (for days with delirium)	ICU LOS: 6 days (9 days for patients with delirium, 5 days for patients without delirium) Mortality: 24% (26% with delirium, 22% without)
van Eijk, 2009[122] CAM-ICU, ICDSC, diagnostic impression of clinician	43 of 126 enrolled (34%)	CAM-ICU: 64 ICDSC: 43 Clinician impression: 29	CAM-ICU: 88 ICDSC: 95 Clinician impression: 96	
van Rompaey, 2007[120] NEECHAM with cut-off score of <20	35 of 172 (20.3%) consecutive patients with NEECHAM, 34 of 172 (19.8%) with CAM-ICU	87	95	ICU LOS 7.0 (mean) (17.5 days for patients with delirium, 5.0 days for patients without delirium)

ICU = intensive care unit; LOS = length of stay; N/A = not applicable; NR = not reported
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

SUMMARY AND DISCUSSION

SUMMARY OF EVIDENCE BY KEY QUESTION

Key Question #1. What is the effectiveness of screening for delirium in adult inpatients?
1a. Do these results vary by medical unit, age, gender or comorbid conditions?
1b. Does screening for delirium improve clinical outcomes?

We identified no randomized controlled trials of screening for delirium in hospitalized patients. There is no direct evidence that screening for delirium is beneficial or harmful. However, universal screening may pose harms, such as misclassification, subsequent treatment of non-delirious patients or misdiagnosis of those with delirium. Opportunity costs include the time to administer screening tests and follow-up (including those of the consultants-typically a psychiatric consult) required for positive results. Additionally, we found no evidence from recent systematic reviews that pharmacologic and non-pharmacologic delirium treatments improve outcomes. Therefore, we conclude that the evidence is insufficient about the net benefit of delirium screening among all hospitalized patients or subgroups of patients as defined by age, gender, comorbidities or admission to intensive care units.

Key Question #2. What are the effectiveness and harms of delirium prevention strategies in acute elderly inpatients?
2a. Do these results vary by medical unit, age, gender or comorbid conditions?

Low level evidence suggests that pharmacologic strategies using analgesia via fascia iliaca compartmental block, antipsychotics, and lighter anesthesia may be useful in delirium prevention. However, there were only a few studies, small in size, examining each category of prevention medications, and more research is needed. Pre-operative administration of statins was not found to effect the incidence of delirium. The evidence for peri-operative use of cholinesterase inhibitors and continuous epidural bupivicaine plus fentanyl versus continuous intravenous fentanyl is mixed.

The evidence shows that multi-component strategies were generally successful in delirium prevention, although these interventions varied widely and often involved multiple strategies and disciplines, making it difficult to determine which components of the multi-component strategies may be effective. The evidence suggests that staff education alone or music therapy may be effective strategies, although there are currently only two studies supporting these interventions. There is no evidence that bright light therapy is an effective strategy for delirium prevention.

The evidence suggests that there are few harms associated with the methods used in these studies for delirium prevention. None of the included studies were stratified by medical unit, age or comorbid conditions. Therefore, we are unable to ascertain whether effectiveness or harms varied by medical unit, age, gender or comorbid conditions.

KEY QUESTION #3. What is the comparative diagnostic accuracy of the tools used to detect delirium:
3a. In elderly medical and surgical inpatients?
3b. In elderly ICU inpatients?

A systematic review of bedside instruments concluded that the CAM was a suitable tool for medical and surgical inpatients, many of whom were evaluated in geriatric units. The ease of administration (completion in less than 5 minutes) was also considered although it was noted that administrators should be trained for optimal use and that the CAM was originally developed for use in conjunction with a formal cognitive assessment. The accuracy of bedside instruments delivered by individuals without training as stand-alone tools for delirium screening is not known. Fewer studies have evaluated the diagnostic accuracy of tools to detect delirium for elderly ICU inpatients. The CAM-ICU, a version of the CAM adapted for use in the ICU, appears to have high specificity but sensitivity varies (ranging from 64 to 100%) indicating that some patients with delirium will not be identified using the CAM-ICU alone. Not all of these studies were restricted to elderly patients and most excluded patients with neurological disease or cognitive dysfunction. Other tools have been evaluated in only one or two studies.

RECOMMENDATIONS FOR FUTURE RESEARCH

The highest future research need is to conduct a randomized trial to evaluate the effectiveness and harms of screening for delirium in adults admitted to hospitals. Enrollment could target individuals likely to be at increased risk for, and thus hopefully at greatest benefit of, successful screening, prevention and treatment options. These could include individuals who are elderly, those with multiple comorbid conditions including mental health and cognitive impairment, and those receiving or likely to receive interventions or medications that can increase the risk of delirium and patients admitted to intensive care units. Additional work is needed to more clearly assess the harms associated with delirium screening and prevention, including the opportunity costs to health service personnel. These opportunity costs include the time and effort to administer screening tools as well as the downstream effects that occur based on follow-up of positive screen results or the efforts required for preventive strategies. More research is needed to verify the findings that some pharmacologic and non-pharmacologic strategies are helpful in the prevention of delirium, particularly in larger and more diverse populations, and with reports stratified by age, medical unit and comorbid conditions. Additionally, more research is needed to start to identify which components of the multi-component non-pharmacologic strategies may be most successful in delirium prevention. Investigations regarding delirium 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 delirium. This research may offer some recommendations for prevention strategies that could easily be implemented. Finally, continued evaluation of diagnostic tools is warranted including the effects of training on diagnostic accuracy and the use of the tools in combination with other (e.g., cognitive) patient assessments.

CONCLUSIONS

Our review of the evidence on screening for and prevention and diagnosis of delirium finds the following:

1. There is insufficient evidence regarding benefits and harms of delirium screening in hospitalized patients including subgroups of patients as defined by age, gender, comorbidities, or ICU admission. We identified no randomized trials of screening for delirium in hospitalized patients. Conducting large pragmatic delirium screening trials is a high-priority research need.
2. There are low quality data regarding pharmacological strategies to prevent delirium. Many proactive preventive strategies have not been examined; those that have are typically reported in only a single trial. In addition, sample sizes are typically small, populations represent only selected groups of patients, and there is little consistency or completeness of outcomes reporting.
3. Multi-component interventions hold promise and are widely used in real world settings but few randomized trials have been reported. The absolute effectiveness and the contributing effectiveness of individual components is not well known but most appear to include some method of staff education to increase awareness of signs/symptoms and encourage reporting of delirium with subsequent earlier intervention.
4. Available diagnostic tests have acceptable diagnostic operating characteristics in the populations and settings where they have been studied and when administered by individuals with adequate training. Concurrent mental status testing may also be a factor in accuracy of diagnosis with these tests. It is not known whether the operating characteristics are robust across a wide range of populations and settings where the prevalence and incidence of delirium varied from the reported studies.
5. Additional research is needed to evaluate the clinical effectiveness and harms of screening, pharmacological and non-pharmacological interventions to prevent delirium applied to a larger and more diverse population, and diagnostic tools used in a broader range of populations and settings.

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