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Delirium: Screening, Prevention, and Diagnosis

A Systematic Review of the Evidence

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VA Evidence-based Synthesis (ESP) Program Overview

- **Sponsored by VA Office of R&D and HSR&D.**
- **Established to provide timely and accurate syntheses/reviews of healthcare topics identified by VA clinicians, managers and policy-makers, as they work to improve the health and healthcare of Veterans.**
- **Builds on staff and expertise already in place at the Evidence-based Practice Centers (EPC) designated by AHRQ. Four of these EPCs are also ESP Centers:**
  - Durham VA Medical Center; VA Greater Los Angeles Health Care System; Portland VA Medical Center; and Minneapolis VA Medical Center.

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- **Provides evidence syntheses on important clinical practice topics relevant to Veterans, and these reports help:**
  - develop clinical policies informed by evidence,
  - the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures, and
  - guide the direction for future research to address gaps in clinical knowledge.
- **Broad topic nomination process – e.g. VACO, VISNs, field – facilitated by ESP Coordinating Center (Portland) through online process:**

http://www.hsrd.research.va.gov/publications/esp/TopicNomination.cfm

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- **Steering Committee representing research and operations (PCS, OQP, ONS, and VISN) provides oversight and guides program direction.**
- **Technical Advisory Panel (TAP)**
  - Recruited for each topic to provide content expertise.
  - Guides topic development; refines the key questions.
  - Reviews data/draft report.
- **External Peer Reviewers & Policy Partners**
  - Reviews and comments on draft report
- **Final reports posted on VA HSR&D website and disseminated widely through the VA.**

http://www.hsrd.research.va.gov/publications/esp/reports.cfm

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Current Report

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

(September, 2011)

Full-length report available on ESP website:

http://www.hsrd.research.va.gov/publications/esp/reports.cfm

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Background

- **Common syndrome**
  - 10-30% of all hospital admissions
  - Over 80% in at-risk populations (e.g., elderly, ICU)
- **Associated with serious outcomes**
  - Mortality, morbidity, length of stay, institutionalization
- **Under-recognized**
- **Many precipitating factors**
  - Medications, diseases, surgical procedures, and environmental factors

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Delirium definition

- **Disturbance in a person's mental abilities that results in a decreased awareness of one's environment and confused thinking**
  - Onset usually sudden-hours to few days (not gradual progressive decline-dementia)

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Delirium Signs and Symptoms

- **Reduced awareness of the environment**
  - Inability to stay focused, wandering attention, stuck on idea, easily distracted
- **Cognitive impairment or poor thinking skills**
  - Poor memory, particularly of recent events
  - Disorientation
  - Difficulty reading, writing, speaking, recalling or understanding
- **Other common symptoms**
  - Seeing things that don't exist (hallucinations)
  - Agitation, irritability, fear, anger, depression, combative behavior
  - Little or no activity or response to environment
  - Disturbed sleep

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Key Questions

Key Question 1

- **What is the *effectiveness* of *screening* for delirium in adult inpatients?**
    - Do these results vary by medical unit, age, gender or comorbid conditions?
    - Does screening for delirium improve clinical outcomes?

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Key Questions

Key Question 2

- **What are the *effectiveness and harms* of delirium *prevention* strategies in acute elderly inpatients?**
    - Do these results vary by medical unit, age, gender or comorbid conditions?

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Key Questions

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 medical or surgical intensive care unit (ICU) inpatients?

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Screening

- **Definition:**
  - Test intended to detect a condition in an individual without signs or symptoms of the index condition
- **Criteria for effective screening**
  - Disease is common, results in substantial morbidity and mortality
  - Detection tools have sufficient accuracy (sensitivity, specificity, PV)
  - Effective interventions exist
  - Detection in asymptomatic phase results in better health outcomes than detection in symptomatic (benefits outweigh harms)
    - Evidence required to recommend screening is generally higher than for tests or treatment of individuals with DZ signs or symptoms:
      - Patients asymptomatic
      - Benefits to few, harms to many

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Assessing Net Benefit

Benefit – Harms = Net Benefit

(Magnitude X Frequency & Timing) – (Magnitude X Frequency & Timing)

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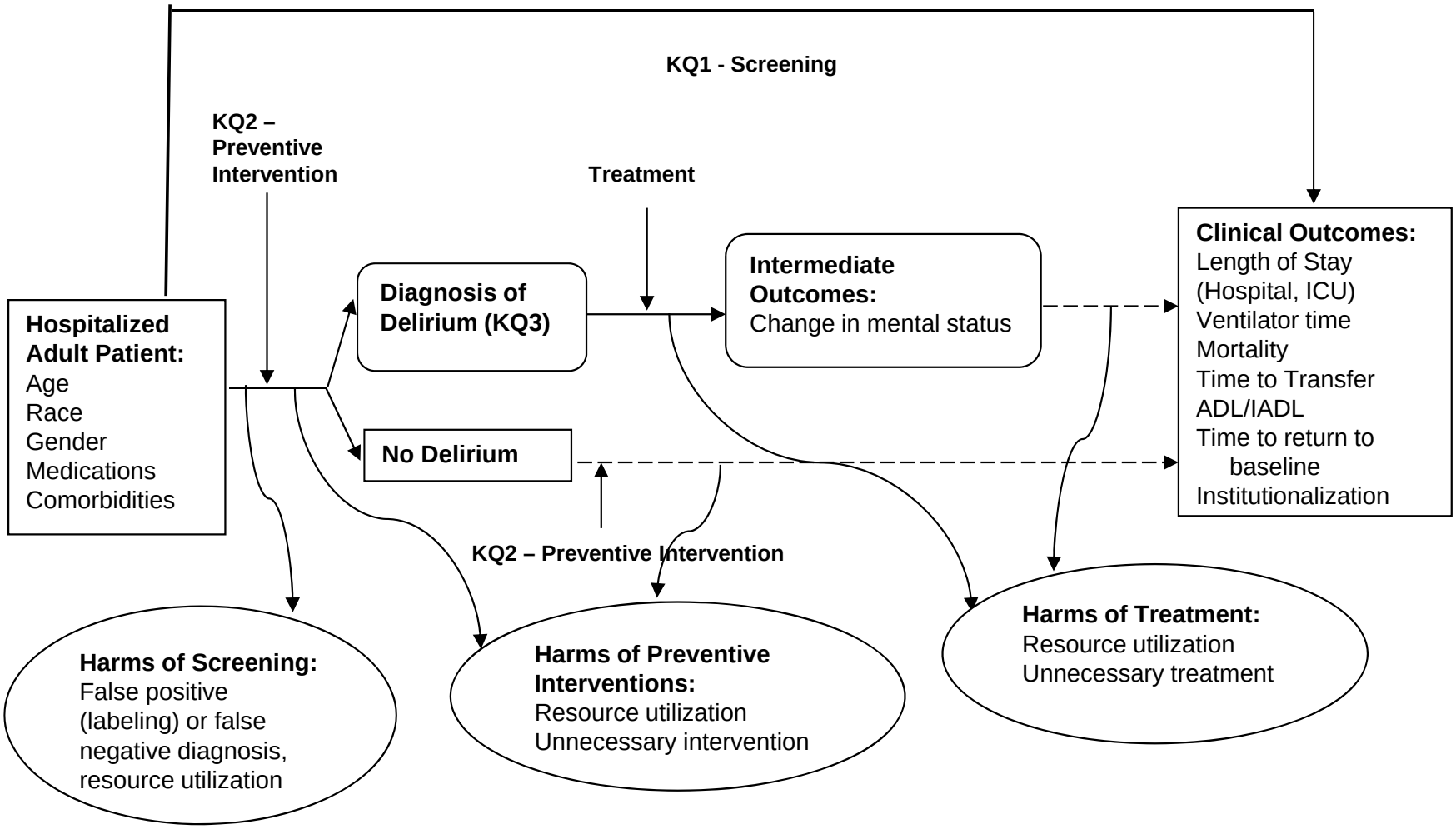
Analytic Framework



Methods

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- **Literature Search:** MEDLINE, CINAHL, PsycINFO; 1950 to November 2010; English language

- **Exclusion criteria for screening / diagnosis questions:**

Age <16 yrs	Alcohol-related delirium	Not hospitalized
No reference standard (e.g., DSM-IV)	Index and reference test by same individual	Case series (n<10) or case report

- **Exclusion criteria for prevention question:**

Age <16 yrs	Nursing home resident	Case series or case report

Methods, continued

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- **Study Quality/Strength of Evidence:**

  RCTs

  a. quality - allocation concealment, blinding, intention-to-treat analysis, reporting of withdrawals/drop-outs (Higgins, 2011)

  b. strength of evidence – risk of bias, consistency, directness, precision (Owens, 2010)

  Diagnostic Accuracy Studies

  a. quality – independent, blinded, criterion standard, large sample of consecutive individuals (Simel, 2008)

  b. strength of evidence – not evaluated due to heterogeneity in approaches

Literature Search Results

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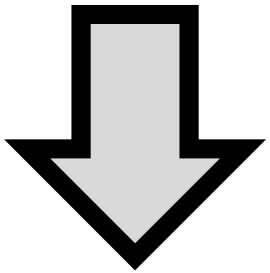
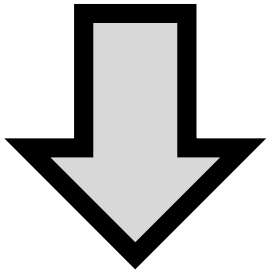


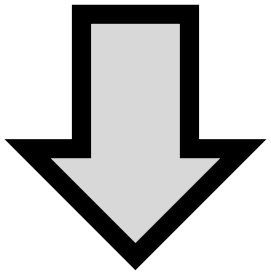
Screening: 1,889 abstracts reviewed (excluded 1778); 111 full text articles reviewed:

Included: 0



Prevention: 1,175 abstracts reviewed (excluded 946); 228 full text articles reviewed (excluded 197); hand search added 8;

Included: 39



Diagnosis (ICU only): 76 abstracts reviewed (excluded 40); 36 full text articles reviewed (excluded 21);

Included: 15

Key Question 1 – Effectiveness of Screening

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- **No studies compared patient outcomes in hospitalized patients randomly (or non-randomly) assigned to screening or no screening for delirium**

- **Potential harms of screening:**
  - misclassification (inappropriate treatment or no treatment, psychological harm to patient and family), opportunity costs (screening and follow-up)

Key Question 2 – Prevention

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- **39 studies, 7935 total patients**

	Randomized	Non-Randomized
Pharmacologic	16	4
Non-pharmacologic	5	14

- **Mean age: 78 years** **Gender: 44% male**
- **Orthopedics/orthopedic surgery: 33% of enrolled patients**
- **Cardiac surgery: 19%**
- **Other surgery: 8%**
- **Internal medicine/geriatrics: 40%**
- **16 studies (53% of enrolled patients) in United States or Canada**

Key Question 2 – Prevention – Pharmacologic RCTs

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Intervention*	RCTs	Risk Ratio (95%CI)	Evidence
Cholinesterase inhibitor	3	0.93 (0.51-1.69)	Low
Atypical antipsychotic	2	0.35 (0.25-0.50)	Moderate
Typical antipsychotic with consultation	1	0.91 (0.59-1.42)	Low
Typical antipsychotic	1	0.32 (0.12-0.91)	Low
Fascia iliaca block	1	0.45 (0.24-0.87)	Low
Continuous epidural vs. continuous intravenous	1	0.87 (0.45-1.69)	Low
Deep vs. light sedation	1	0.48 (0.26-0.89)	Low
Ketamine bolus	1	0.11 (0.02-0.82)	Low
Regional vs. general anesthesia	1	0.74 (0.21-2.59)	Low
Epidural vs. general anesthesia	1	1.32 (0.73-2.39)	Low
Dexmedetomidine vs. propofol or midazolam	1	0.23 (0.08-0.61) (P) 0.24 (0.09-0.64) (M)	Low
Delirium free protocol vs. usual care	1	0.14 (0.02-1.06)	Low
Melatonin	1	0.37 (0.17-0.81)	Low
*versus placebo except where indicated			

Key Question 2 – Prevention – Cholinesterase Inhibitor RCTs - Pooled

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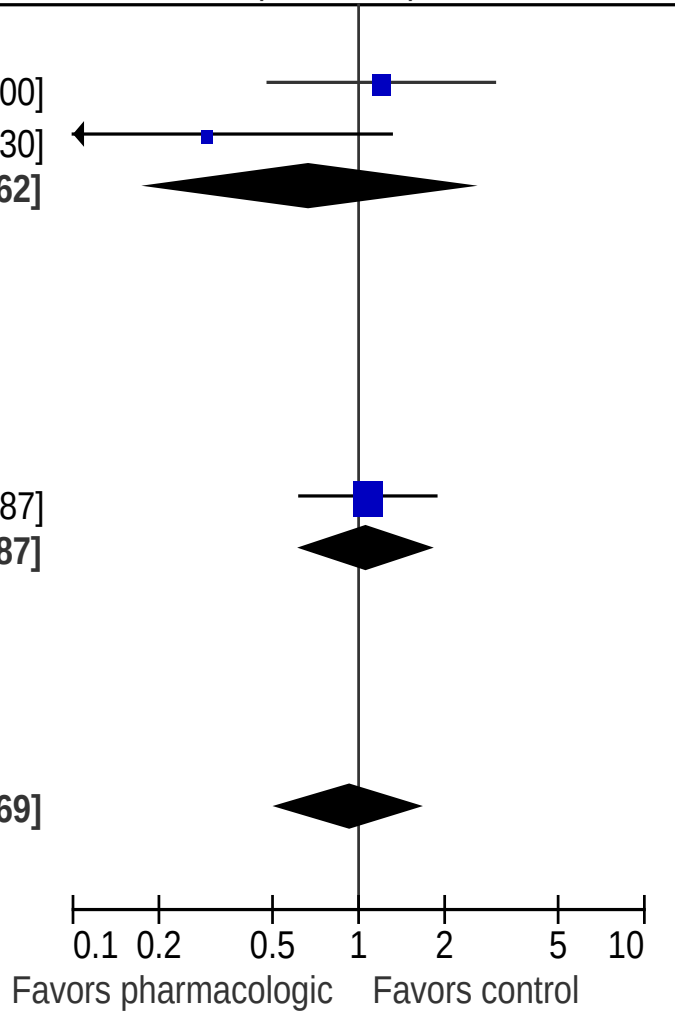
Study or Subgroup	Pharmacologic Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Donepezil versus placebo						
Liptzin 2005	8	39	7	41	30.4%	1.20 [0.48, 3.00]
Sampson 2007	2	19	5	14	14.0%	0.29 [0.07, 1.30]
Subtotal (95% CI)		**58**		**55**	**44.5%**	**0.68 [0.17, 2.62]**
Total events	10		12			
Heterogeneity: $Tau^2 = 0.59$; $Chi^2 = 2.50$, df = 1 (P = 0.11); $I^2 = 60\%$						
Test for overall effect: Z = 0.57 (P = 0.57)						
1.1.2 Rivastigimine versus placebo						
Gamberini 2009	18	56	17	57	55.5%	1.08 [0.62, 1.87]
Subtotal (95% CI)		**56**		**57**	**55.5%**	**1.08 [0.62, 1.87]**
Total events	18		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.79)						
Total (95% CI)		**114**		**112**	**100.0%**	**0.93 [0.51, 1.69]**
Total events	28		29			
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 2.83$, df = 2 (P = 0.24); $I^2 = 29\%$						
Test for overall effect: Z = 0.24 (P = 0.81)						
Test for subgroup differences: $Chi^2 = 0.39$, df = 1 (P = 0.53), $I^2 = 0\%$						



Key Question 2 – Prevention – Atypical Antipsychotic RCTs – Pooled

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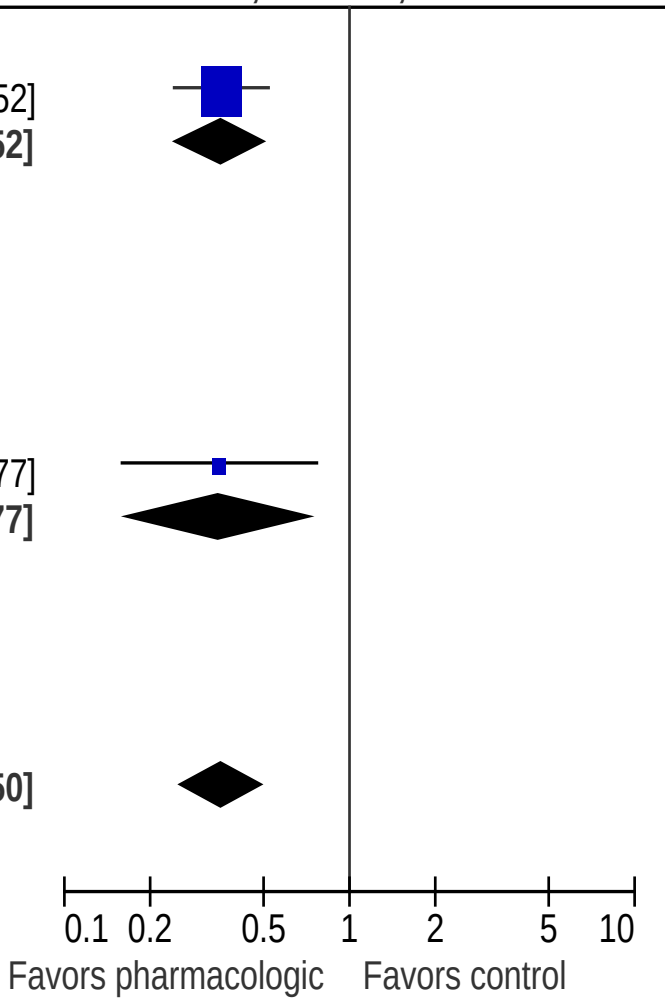
Study or Subgroup	Pharmacologic Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.2 Olanzapine (atypical antipsychotic) versus placebo: Orthopedic patients						
Larsen 2010	28	196	82	204	81.0%	0.36 [0.24, 0.52]
Subtotal (95% CI)		**196**		**204**	**81.0%**	**0.36 [0.24, 0.52]**
Total events	28		82			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.31 (P < 0.00001)						
1.5.3 Risperidone (atypical antipsychotic) versus placebo: Cardiac surgery patients						
Prakanrattana 2007	7	63	20	63	19.0%	0.35 [0.16, 0.77]
Subtotal (95% CI)		**63**		**63**	**19.0%**	**0.35 [0.16, 0.77]**
Total events	7		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.62 (P = 0.009)						
Total (95% CI)		**259**		**267**	**100.0%**	**0.35 [0.25, 0.50]**
Total events	35		102			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.00$, df = 1 (P = 0.97); $I^2 = 0\%$						
Test for overall effect: Z = 5.92 (P < 0.00001)						
Test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 0.97), $I^2 = 0\%$						



Key Question 2 – Prevention – Pharmacologic Non-RCTs

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- **Cholinesterase Inhibitors – 2 studies, different medications (rivastigmine, physostigmine), geriatric medicine or elective surgery patients, significant reduction in risk in both studies**

- **Analgesia – 1 study, patient controlled femoral nerve vs. intravenous, orthopedic patients, significant reduction in risk**

- **Anti-lipid therapy – 1 study, statin vs. no statin, cardiac surgery patients, no significant difference in risk**

Key Question 2 – Prevention – Non-Pharmacologic Studies

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Multi-component Intervention Studies

	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
RCTs (n=3)	1	2	3	2	1	2	1	3	2
Non-RCTs (n=13)	8	9	12	7	5	10	6	8	7

Studies not pooled due to heterogeneity of interventions

Key Question 2 – Prevention – Non-Pharmacologic Studies

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- **3 Multi-Component RCTs**
  - Significantly lower incidence of delirium in 2 of 3 studies
    - 1 was moderate quality
  - Relative risks: 2 of 3 studies had reduced risk
    - moderate quality study was significant

- **13 Multi-Component Non-RCTs**
  - Significantly lower incidence of delirium in 10 of 12 studies reporting significance
  - Relative risks: all studies had reduced risk; 7 significant

Key Question 2 – Prevention - Non-Pharmacologic Studies

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- **Single Component Studies**
- **2 RCTs – (low quality)**
  - Bright light:– non-significant reduction in delirium incidence
  - Music added to usual care – reduction in delirium incidence
- **1 Non-RCT –**
  - Staff education –reduction delirium incidence

Key Question 2 – Prevention Harms

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- **Mortality**
  - Reported in 7 pharmacologic and 11 non-pharmacologic studies
  - 1 study: significantly lower mortality in intervention group

- **Adverse Events**
  - 13 pharmacologic and 7 non-pharmacologic studies
  - Few significant differences
  - Pharmacologic studies (n=2): Mixed results for use of restraints
  - Non-pharmacologic studies (n=3): fewer bed sores
  - Non-pharmacologic studies (n=2): fewer falls
  - Non-pharmacologic study (1 each): reduced infection, pain, bedridden status, restraint use

Confusion Assessment Method (CAM) Diagnostic Algorithm

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- **Feature 1: Acute onset and fluctuating course**
  - Change in mental status from baseline; behavior fluctuating in past day
- **Feature 2: Inattention**
  - Easily distracted; difficulty keeping track of what was being said
- **Feature 3: Disorganized thinking**
  - Speech disorganized or incoherent; illogical flow of ideas; switching from subject to subject
- **Feature 4: Altered level of consciousness**
  - Alert, vigilant, lethargic, stupor, coma

Diagnosis: present/abnormal rating for features 1 and 2 and also for either feature 3 or 4

Key Question 3 – Diagnosis Non-ICU Patients

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- **Systematic review (Wong, JAMA 2010)**
  - Included 25 studies; 15 with elderly patients
    - Hospitalized patients (non-ICU)
    - Appropriate reference standard (DSM-IV or similar) performed by specialist
    - Adult, non-alcohol related delirium
  - CAM – most widely studied (12 studies, 1,036 patients)
    - Sensitivity 86%, Specificity 93% (pooled)
    - Likelihood ratios: positive test = 9.6 negative test = 0.16
    - Considerable heterogeneity (I^2 > 65%)
  - Other tools with more than 1 study
    - Delirium Rating Scale (4 studies, 943 patients)
    - Memorial Delirium Assessment Scale (3 studies, 330 patients)
    - Delirium Observation Screening Scale (2 studies, 178 patients)

Key Question 3 – Diagnosis ICU Patients

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- **Diagnosis in Elderly ICU Patients**
  - 15 studies; 1,272 medical, surgical, or psychiatric patients; 4 studies included intubated patients
  - 11 different tools/methods for diagnosis
  - CAM-ICU: (6 studies)
    - Sensitivity: 64-100% Specificity: 88-100%
  - Intensive Care Delirium Screening Checklist (ICDSC): (2 studies)
    - Sensitivity: 43-99% Specificity: 64-95%
  - Other tools (all 1 study)
    - Sensitivity: 30-100% Specificity: 64-96%

Summary & Conclusions

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- **SCREENING – Key Question 1**
  - No RCTs (or non-RCTs) of screening for delirium in hospitalized patients
  - Insufficient evidence about net benefit of screening hospitalized patients or subgroups (age, gender, comorbidities, ICU)

Summary & Conclusions

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- **PREVENTION – Key Question 2**
  - Pharmacologic interventions: Low or mixed evidence
    - 1 trial, small, inconsistent outcome reporting
  - Multi-component interventions:
    - generally successful; few RCTs; difficult to determine effective components
  - Harms-few
  - No studies stratified by age, gender, or comorbid conditions

Summary & Conclusions

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- **DIAGNOSIS – Key Question 3**
  - Systematic review:
    - CAM: suitable operating characteristics in medical and surgical inpatients
      - Administrator training and concurrent mental status testing may influence accuracy
  - Fewer studies in ICU patients
  - Unknown whether operating characteristics of diagnostic tests are robust across wide range of populations and settings

Future Research Needs

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- **RCTs of delirium screening in hospitalized patients**
- **Assessment of prevention strategies**
  - Pharmacologic
  - Multi-component
- **Assessment of bedside diagnostic tools in broad clinical settings**

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Questions?

If you have further questions, feel free to contact:

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