Table 2. Summary Table of Guidelines (ordered by strength of recommendation)*			
Recommendation Statement	Strength of Recommendation	Quality of Evidence	References
Strong Recommendations			
II. Healthcare systems and hospitals should implement multicomponent nonpharmacologic intervention programs delivered by an interdisciplinary team (including physicians, nurses, and possibly other healthcare professionals) for the entire hospitalization in at-risk older adults undergoing surgery to prevent delirium.	Strong	Moderate	Inouye 1999 Inouye 2000 Holt 2013 Martinez 2012 Rubin 2006 Bjorkelund 2010 Vidan 2009 Inouye 2000 Lundstrom 2007 Chen 2011 Inouye 2003
I. Healthcare systems and hospitals should implement formal educational programs with ongoing formal and/or informal refresher sessions for healthcare professionals on delirium in at-risk older surgical adults to improve understanding of its epidemiology, assessment, prevention, and treatment.	Strong	Low	Lundstrom 2005 Tabat 2005 Robinson 2008
IV. The healthcare professional should perform a medical evaluation, make medication and/or environmental adjustments, and order appropriate diagnostic tests and clinical consultations after an older adult has been diagnosed with postoperative delirium to identify and manage underlying contributors to delirium.	Strong	Low	Heymann 2010 Milisen 2001 Pitkala 2006 Mudge 2013 Young 2003
VIII. Healthcare professionals should optimize postoperative pain control, preferably with nonopioid pain medications, to minimize pain in older adults to prevent delirium.	Strong	Low	Vaurio 2006 Lynch 1998 Leung 2006 Krenk 2012
IX. The prescribing practitioner should avoid medications that induce delirium postoperatively in older adults to prevent delirium.	Strong	Low	Agostini 2001 Marcantonio 1994 Taipale 2012 Luukkanen 2011
XI. In older adults not currently taking cholinesterase inhibitors, the prescribing practitioner should not newly	Strong	Low	Gamberini 2009 Liptzin 2005

	prescribe cholinesterase inhibitors perioperatively to older adults to prevent or treat delirium.			Marcantonio 2011 Sampson 2007 Overshott 2010 Van Eijk 2010
XIII.	The prescribing practitioner <u>should not</u> use benzodiazepines as a first line treatment of the agitated post-operative delirious patient who is threatening substantial harm to self and/or others <u>to treat postoperative delirium</u> *except* when benzodiazepines are specifically indicated (including but not limited to treatment of alcohol or benzodiazepine withdrawal). Treatment with benzodiazepines should be at the lowest effective dose for the shortest possible duration, and should be employed only if behavioral measures have failed or are not possible and ongoing use should be evaluated daily with in-person examination of the patient.	Strong	Low	Breitbart 1996 Marcantonio 1994 Pisani 2009 Pandharipande 2006
XIV.	The prescribing practitioner <u>should not</u> prescribe antipsychotic or benzodiazepine medications for the treatment of older adults with postoperative delirium who are not agitated and threatening substantial harm to self or others.	Strong	Low	Hakim 2012 Girard 2010 Breitbart 1996
Weak Recommendations				
III.	Healthcare professionals should consider multicomponent interventions implemented by an interdisciplinary team in older adults diagnosed with postoperative delirium to improve clinical outcomes.	Weak	Low	Lundstrom 2005 Zaubler 2013 Rubin 2006 Inouye 2000 Lundstrom 2007 Milisen 2001 Rubin 2011 Cole 1994 Cole 2002 Mador 2004 Marcantonio 2010 Pitkala 2006 Schweikert 2009
VII.	A healthcare professional trained in regional anesthetic injection may consider providing regional anesthetic at	Weak	Low	Mouzopoulos 2009 Kinjo 2012

	the time of surgery and postoperatively to improve pain control and prevent delirium in older adults.			
XII.	The prescribing practitioner may use antipsychotics at the lowest effective dose for the shortest possible duration to treat patients who are severely agitated or distressed, and are threatening substantial harm to self and/or others. In all cases, treatment with antipsychotics should be employed only if behavioral interventions have failed or are not possible, and ongoing use should be evaluated daily with in-person examination of patients.	Weak	Low	Hakim 2012 Girard 2010 Devlin 2010 Tahir 2010 Maneeton 2013 Han 2004 Grover 2011 Kim 2010 Skrobik 2004 Yoon 2013 Breitbart 1996
Recommendations Without Sufficient Evidence				
VI.	The anesthesia practitioner may use processed electroencephalographic (EEG) monitors of anesthetic depth during intravenous sedation or general anesthesia of older patients to reduce postoperative delirium.	Insufficient	Low	Sieber 2010 Santarpino 2011 Chan 2013 Radtke 2013
X.	There is insufficient evidence to recommend for or against the use of antipsychotic medications prophylactically in older surgical patients to prevent delirium.	Not Applicable	Low	Larsen 2010 Van den Boogaard 2013 Prakanrattana 2007 Wang 2012 Kaneko 1999 Page 2013 Vochteloo 2011 Kalisvaart 2005
V.	There is insufficient evidence to recommend for or against hospitals creating, and healthcare professionals using, specialized hospital units for the inpatient care of older adults with postoperative delirium to improve clinical outcomes.	Not Applicable	Low	Bee Gek Tay 2013 Eeles 2013 Flaherty 2010 Lu 2011 Goldberg 2013

G3-G5-Inouye SK, Bogardus ST, Jr., Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med. 1999;340(9):669-76.

Study Characteristics	Population	Intervention Groups	Results		Comments
			Measure	Outcome	
Inouye 1999 **USA** **Setting** General medicine service at a teaching hospital **Study Design** Controlled clinical trial using prospective individual matching **Selection method** Consecutive patients admitted to the general-medicine service at urban teaching hospital **Study Length/Start-Stop Dates** 3/1995 – 3/1998 **Purpose** To compare the effectiveness of a multicomponent strategy for reducing the risk of delirium with that of a usual plan of care for hospitalized older patients, to determine the level of adherence to the intervention protocol, and to measure the effect of the intervention on the targeted risk factors. **Funding source(s):** Grants from NIA, Commonwealth Fund, Retirement Research Foundation, Community Foundation for Greater New Haven **Quality Score**: 7 **Risk of Bias**: Unclear	**N = 2434 potentially eligible** n = 1169 eligible n=250 patient, family or physician refused enrollment n=67 matching patient not found **N=852 final study sample** n=426 pairs of patients receiving study intervention and usual care (see matching procedures in Comments column) **Inclusion** Age≥70 -no delirium at admission -intermediate or high risk for delirium at base line **Exclusion** N = 1265 -inability to participate in interview n= 154 profound dementia that precluded verbal communication n=92 language barrier n=38 profound aphasia n=14 intubation or respiratory isolation n-69 coma or terminal illness n=219 hospital stay 48h or less n=324 prior enrollment in this study n=355 other reasons like **Excluded patients** did not differ significantly from the 852 patients who were enrolled in terms of age, sex, or base-line risk of delirium -larger proportion of patients receiving usual care were excluded (63 percent, vs. 50 percent in the intervention group; P=0.001	**n = 426 intervention** Men and women (61%) Mean age 79.6 (6.1) MMSE = 23.7 (4.6) MMSE <24 = 41% Risk of delirium intermediate = 72% Risk of delirium high = 28% **Protocol** 1) Elder Life Program was implemented by a trained interdisciplinary team, which consisted of -a geriatric nurse-specialist, -two specially trained Elder Life specialists, -a certified therapeutic-recreation specialist, -a physical- therapy consultant, -a geriatrician, -trained volunteers. 2) Six risk factors for delirium were targeted for intervention: -cognitive impairment, -sleep deprivation, - immobility, -visual impairment, - hearing impairment, -dehydration 3) adherence to intervention recorded daily	**Delirium assessment:** MMSE CAM **Delirium severity** (additive score of 4) -symptom fluctuation -inattention -disorganized thinking -altered level of consciousness **Baseline characteristics** **Primary outcomes** Delirium **Secondary outcomes** Total number of days of delirium No. episodes of delirium Overall rate of adherence Cognitive impairment improved by 2 points Adjusted orientation score at reassessment Use of sedative drug for sleep during hospital stay Total number of risk factors, improved (fewer risk factors) Adjusted no. risk factors per patient at reassessment	- MMSE, CAM evaluated daily by research nurses and experienced clinical researchers; Hospital day 5 or at discharge (if before day 5) patients reassessed for risk factors of delirium; Delirium severity assessed by sum of scores = delirium severity no significant differences between groups No significant difference between groups Of all baseline assessments, only MMSE <24 was associated with outcome p<0.01 **intervention vs. usual-care** 9.9% vs. 15% p = 0.02 105 days vs. 161 days p = 0.02 62. vs. 90 p = 0.03 87% (8716 of 10,056 patient-days) 51(40%) vs. 33(26%) p = 0.04 7.2(0.2) vs. 6.8(0.2) p=0.06 148 (35%) vs. 195 (46%) p=0.001 272 (64%) vs 236(55%) p=0.02 1.7(0.1) vs. 1.9(0.1) p=0.001	**Cost of intervention** Total = $139,506 $327 per patient in intervention group The cost of intervention per case of delirium prevented was $6,341 ($139,506 for 22 cases prevented [64 cases of delirium occurred in patients receiving usual care, as compared with 42 cases in those receiving the intervention]). **Comments** Intervention was most effective in patients who were at intermediate risk for delirium at base line. Once an initial episode of delirium had occurred, however, the intervention had no significant effect on the severity of delirium or on the likelihood of recurrence. This finding has an important implication for the treatment of delirium: primary prevention is probably the most effective strategy **Matching procedures** -computerized algorithm designed to match patients according to -age within five years, -sex, -base-line risk of delirium (intermediate or high) **Predictive model (4 risk factors)** **-** visual impairment, -severe illness, -cognitive impairment, -high ratio of blood urea nitrogen to creatinine. **Intermediate risk** -presence of 1 or2 risk factors at base line, **High risk** -presence of 3 or4 risk factors at base line
		n = 426 usual care Men and women (61%) Mean age 79.8 (6.2) MMSE 23.3 (4.9) MMSE <24 45% Risk of delirium intermediate 72% Risk of delirium high 28% **Protocol** **-**standard hospital services provided by physicians, nurses, and support staff in other general-medicine units. -members of the intervention team did not provide services - same attending and resident physicians provided care to patients in both study groups	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Secondary outcomes**	See above See above See above See above	
Conclusion: The risk-factor intervention strategy that we studied resulted in significant reductions in the number and duration of episodes of delirium in hospitalized older patients. The intervention had no significant effect on the severity of delirium or on recurrence rates; this finding suggests that primary prevention of delirium is probably the most effective treatment strategy.					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	1	Low	
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	Unclear	Possible contamination, intervention protocols disseminated by word of mouth to usual care unit staff. Physicians carried over some intervention protocols to usual-care group
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = Unclear**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 7**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G3-G5-Inouye SK. Prevention of delirium in hospitalized older patients: risk factors and targeted intervention strategies. Ann Med. 2000a;32(4):257-63.

Study Characteristics	Population	Studies	Results		Other information
			Measure	Outcome	
Inouye 2000a **USA** **Setting** General medicine service at a university hospital **Study Design** -prospective studies to examine predisposing and precipitating factors for delirium, -controlled clinical trial intervention using prospective individual matching **Selection method** Delirium Prevention Trial: consecutive patients admitted to general medicine service at university hospital **Study Length/Start-Stop Dates** Not discussed **Purpose** To describe the multifactorial etiology of delirium; to elucidate the predisposing and precipitating factors for delirium derived from earlier work; and to present an overview of the Delirium Prevention Trial, which was targeted to address delirium risk factors. **Funding source(s):** Grants from NIA and Patrick and Catherine Weldon Donaghue Medical Research Foundation **Quality Score**: 7 **Risk of Bias**: Unclear	**Delirium Prevention Trial** **N = 852 enrolled** n=426 matched pairs of intervention-control patients . **Inclusion** Age ≥ 70 -no evidence of delirium at admission -intermediate to high risk for delirium at baseline **Exclusion** Not discussed ****** **Delirium Prevention Trial** Prospective matching strategy to assure comparability of patients between intervention and control groups **Protocols for targeted risk factors** Cognitive impairment -reality orientation -therapeutic activities Sleep deprivation -noise reduction -uninterrupted slep Immobility -early mobilization -minimize immobilizing equipment Visual impairment -vision aids -adaptive equipment Hearing impairment -amplifying devices -hearing aids -wax disimpaction Dehydration -early recognition -volume repletion	*To identify predisposing factors for developing of delirium during hospitalization* **n = 107 patients first cohort** **n = 174 second cohort** **(validated first cohort findings)** **Inclusion** Age ≥ 70 -admitted to general medicine service at a university hospital	>30 potential risk factor variables studied **Predisposing risk factors** Vision impairments (acuity <20/70) Severe illness (APACHE II >16) Cognitive impairment (MMSE <24) Dehydration (BUN/CR ratio ≥ 18(	 RR 3.5 (1.2 – 10.7) RR 3.5 (1.5 – 8.2) RR 2.8 (1.2 – 6.7) RR 2.0 (0.9 – 4.6)	Patients placed in low (no factors present), intermediate (one or two factors present), or high (three or four factors present) risk groups showed a statistically significant trend towards increasing risk of delirium with increasing numbers of predisposing factors. RR for delirium increased from 1.0 in low-risk group to 9.2 in high-risk group. -predictive model and risk stratification system validated in the second cohort of patients
		Examine precipitating factors for delirium during hospitalization. Two prospective cohorts of consecutive patients aged 70 years and older admitted to general medical service **n = 196 first cohort** **n = 312 second cohort** **Inclusion** Age ≥ 70 -admitted to general medicine service at a university hospital	Develop and validate a predictive model for delirium based on noxious insults or factors occurring during hospitalization >25 candidate risk factor variables studied **Precipitating factors** Use of physical restraints Malnutrition More than 3 medications added Use of bladder catheter Any iatrogenic event	 RR 4.4 (2.5 – 7.9) RR 4.0 (2.2 – 7.4) RR 2.9 (1.6 – 5.4) RR 2.4 (1.2 – 4.7) RR 1.9 (1.1 – 3.2)	Study demonstrated distinct risk gradients, with patients placed in low, intermediate, or high-risk groups showing a statistically significant trend towards increasing risk of delirium with increasing numbers of precipitating factors. RR for delirium increased from 1.0 in the low-risk group to 22.7 in the high-risk group. -validated in the second cohort of patients which produced similar, statistically significant risk gradients.
		Intervention group = 426 **Delirium Prevention Trial Intervention (Hospital Elder Life Protocol)** **Intervention (see Protocols for targeted risk factors)** Standardized protocols targeted towards six delirium risk factors. **Delirium assessment: Assessment tool: CAM** All patients assessed daily by RAs who had no role in the intervention unaware of intervention or study group assignment **Control Group = 426** Protocol = Usual care with daily delirium assessment	Incidence of delirium Days of delirium Total no. episodes of delirium Rate of adherence to all intervention protocols Adherence rate for individual intervention protocols Intervention resulted in a significant reduction in the total number of risk factors per patient compared with the usual care group at reassessment Improvement in the orientation score of patients with cognitive impairment at admission Reduction in the rate of use of sleep medications in all patients	**Intervention vs. control** 9.9% vs. 15% OR .6 (0.39-.92) 105 vs. 161 p = 0.02 62. vs., 90 p = 0.03 87% 71% - 96% p = 0.001 40% vs 26% improved; p = 0.04 46% vs 35%; p = 0.001 NOTE: Specific recommendations for delirium prevention detailed in PDF	No adverse effects were associated with any intervention protocols Through the identification of risk factors and targeting intervention strategies towards them, we have been successful in preventing delirium in hospitalized older patients, reducing the risk of delirium by 40%. Results suggest that primary prevention of delirium, (preventing delirium before it occurs), may be the most effective treatment strategy for delirium, a finding which holds substantial clinical and health policy implications for delirium management in specific and for the geriatric population more generally.
Conclusion: Through the identification of risk factors and targeting intervention strategies towards them, we have been successful in preventing delirium in hospitalized older patients, reducing the risk of delirium by 40%.					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	Unclear	Not discussed
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	1	Low	
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = Unclear**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 7**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

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  - **Low** risk of bias: Low risk of bias on all 6 domains
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  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G3-Holt R, Young J, Heseltine D. Effectiveness of a multi-component intervention to reduce delirium incidence in elderly care wards. Age Ageing. 2013;42(6):721-7.

Study Characteristics	Population	Intervention Groups	Results		Other Information
			Measure	Outcome	
Holt 2013 **United Kingdom** **Setting** Specialist acute elderly care wards at general hospitals **Study Design** Pre/post study **Selection method** Patients admitted to one of three specialist elderly care wards **Study Length/Start-Stop Dates** 10/2007 – 1/2009 **Purpose** To examine the effect of a multi-component, delirium prevention intervention on rates of incident delirium for patients admitted to specialist elderly care wards **Funding source(s):** Research grant from Research into Ageing **Quality Score:** 4 **Risk of Bias**: High	<u>Before group</u> N = 1123 admitted to study wards <u>After group</u> N = 1039 admitted to study wards **Inclusion** Patients with acute medical illness admitted from Accident and Emergency department or directly by general practitioners to one of three specialist elderly care wards **Exclusion (before group)** N = 907 n = 33 prevalent delirium at baseline n = 752 too unwell to be assessed (in the opinion of clinical staff) n = 122 unable to communicate (dysphasia, unable to speak English) or obtain consent within 24 h of ward admission **Exclusion (after group)** N = 884 n = 32 prevalent delirium at baseline n = 758 too unwell to be assessed (in the opinion of clinical staff) n = 94 unable to communicate (dysphasia, unable to speak English) or obtain consent within 24 h of ward admission **Delirium risk factors targeted** Disorientation Dehydration Visual/hearing impairment Constipation Pain Immobility	**n = 149 before group (10/2007 to 3/2008)** **n = 210 analyzed** n – 3 Lost to follow up n = 207 analyzed at 6 mo follow up. Men and women (65.7%) Mean age 85 (6.01) **Protocol** Usual care (Comprehensive Geriatric Assessment and multidisciplinary care) **Baseline assessments (all patients)** Demographics Dehydration Creatinine Acute illness severity Comorbidity Medications Mobility Visual or hearing impairment Cognitive impairment (MMSE) CAM – 4 item version DRS-R-98	**Delirium assessment:** MMSE CAM(4-tem) DRS-R-98 **Baseline characteristics** Gender (% male) Resident in LTC prior to admission Dehydration urea/creatinine ratio > 0.073 Hearing impairment **Primary outcomes** Patients developing incident delirium during first 7 days after admission to study ward Adjusted for baseline imbalances **Secondary outcomes** Duration of delirium during first 7 days Severity of delirium during first 7 days Hospital readmission w/in 6 mo following discharge **Process outcomes**	Delirium assessed daily by trained research assistants using CAM, DRS-R-98 -assistants blind to baseline assessments -inter-rater reliability was monitored 4 weeks during the study **Before group vs. after group** 34.3% vs. 50% p = 0.003 13.3% vs. 4.6% p = 0.006 68.1% vs. 77.6% p = 0.046 59% vs. 71.7% p = 0.013 **Before group vs. after group** 13.3% vs. 4.6% p = 0.006 OR 3.665(1.40-9.591) p = 0.008 0.29 days (.931) vs. 0.06days(2.87) p = 0.002 16.86(4.92) vs. 9.17(7.94) p = 0.005 41.1% vs. 54.1% p = 0.02 *see Other Information Column*	Delirium incidence, duration and severity were all significantly reduced during the intervention implementation phase of the study. The reduction in delirium persisted after adjustment for differences in baseline delirium risk and demographic variables. **Process outcomes** Delirium education sessions attendance: 70% of staff Healthcare assistants and staff nurses who had increased knowledge about delirium: 82% Recorded adherence to delirium risk factor modification protocols: (27-57%) Protocol adherence was highest for reorientation and hydration, and lowest for mobility and constipation.
		n = 187 after group (8/2008 to 01/2009 **n = 152 analyzed** n = 4 lost to follow up n = 148 analyzed at 6 mo. follow up Men and women (50%) Mean age 85.8 (5.39) **Protocol** Usual care plus delirium prevention intervention: (1) Identification of local opinion leaders or 'champions' to lead the implementation of the intervention. (2) An initial educational intervention to raise awareness, knowledge and enthusiasm. (3) A practice change intervention directed at delirium risk factors.	**Delirium assessment:** **Baseline characteristics/measures** **Primary outcomes** **Secondary outcomes**	See above See above See above See above	

Key Points: 1) Delirium is common in older people admitted to specialist elderly care wards. 2) It is uncertain if multi-component, delirium prevention interventions reduce incident delirium on specialist elderly care wards. 3) Delirium incidence was significantly reduced following a multi-component prevention intervention on elderly care wards.

Conclusion: A multi-component, delirium prevention intervention directed at delirium risk factors and implemented by local clinical staff can reduce incidence delirium on specialist elderly care wards.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	Significant differences between groups
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	Pre/post design
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	RAs only blinded to baseline assessment, not outcome assessments
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	Low	Pre/post design; historical controls Potential confounding variables due to changes in practice not recorded by the study team that may have affected rates of delirium
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 4**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G3-Martinez FT, Tobar C, Beddings CI, et al. Preventing delirium in an acute hospital using a non-pharmacological intervention. Age Ageing. 2012;41(5):629-34.

Study Characteristics	Population	Intervention Groups	Results		Comments
			Measure	Outcome	
Martinez 2012 **Chile** **Setting** Internal medicine ward at a hospital **Study Design** Single blind Randomized controlled clinical trial **Randomization method** Computer-generated random numbers **Study Length/Start-Stop Dates** 9/2009 – 6/2010 **Purpose** To determine whether a non-pharmacological intervention delivered by family members could reduce the incidence of delirium, as compared with standard management of elderly inpatients at intermediate or high risk of developing this condition during the course of hospitalization. **Funding source(s):** Not discussed **Quality Score** 5 **Risk of Bias**: High	**N = 1285 eligible** n = 294 did not meet inclusion criteria n = 287 randomized **Inclusion** Patients with at least one risk factor for delirium from a clinical prediction rule: -Age > 70 -Hx cognitive impairment documented and MMSE < 24 prior to hospitalization -alcoholism or metabolic imbalances at moment of admission **Exclusion** N = 704 n = 434 not hospitalized in general ward n = 181 placed in a room with more than 2 beds (to prevent interference w/ non-pharm intervention) n = 23 family members unavailable n = 11 declined to participate n = 6 safety reasons n = 15 delirium at initial visit n = 34 not randomized/earthquake **Delirium risk factors** Age >70 Previous history of cognitive impairment in medical record (MMSE <24 Alcoholism Metabolic imbalances	**n = 144 Intervention group** Men and women (42%) Mean age 78.1 (6.3) **Protocol** Carried out by patient's family: (i) Education: the observers conducted brief interviews with each patient's family members, in which the main aspects regarding the clinical features and prognostic implications of acute confusional syndromes were explained. These interviews lasted no more than 10 min overall and were accompanied by a specially designed pamphlet. (ii) Provision of a clock (analogue or digital as required by the patient) and calendar in the room. (iii) Avoidance of sensory deprivation (glasses, denture and hearing aids must be available as needed). (iv) Presence of familiar objects in the room (photographs, cushions and radio). (v) Reorientation of patient provided by family members (current date and time, recent events). (vi) Extended visitation times (5 h daily).	**Delirium assessment:** CAM **Baseline characteristics** **Primary outcomes** Incident delirium (breakdown by type) Mixed delirium Hypoactive delirium Hyperactive delirium **Secondary outcomes** Falls	CAM administered daily by three trained observers who had validated each other to Fleiss kappa statistic (K = 1) -Observers did not diagnose cognitive impairment and dementia diagnosed based solely on chart review No significant differences **Intervention vs. control** **N = 144 vs 143** 5.6% vs. 13.3% RR 0.41(0.19-0.92) p = 0.027 RR reduction of developing delirium 59% 1.4% vs. 6.3% 1.4% vs. 5.6% 2.8% vs. 1.4% 0% vs. 2.8% p = 0.06	**Lost to follow-up (all analyzed)** n = 4 in intervention group n = 9 in control group The most important difference in outcomes was a moderate tendency towards a delayed onset of delirium in our study, which could also be a consequence of the non-pharmacological intervention. The incidence of dementia was low, roughly affecting 6% of the included patients, as was the prescription of high-risk medications during the hospital stay, present in just about the same proportion (5%). Both these findings are surprising, considering the important role that they play as predisposing and triggering factors of delirium, respectively, and should be kept in mind when analyzing results. Reasons could be: -patients with present delirium excluded from study -patients with moderate to advance stages of dementia are admitted to special care wards not suitable for study comparisons
		n = 143 control group Men and women (33%) Mean age 78.3 (6.1) **Protocol** Usual care	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Secondary outcomes**	See above See above See above See above	
Key Points: 1) Delirium is a common neuropsychiatric syndrome that is most frequently seen in elderly patients. 2) It has been associated with increased morbidity and mortality, functional impairment, cognitive decline and increased health-care costs. 3) In this study, a multicomponent intervention delivered by family members significantly reduced the incidence of delirium in a group of elderly medical inpatients.					
Conclusion: Our non-pharmacological intervention carried out by family members reduced the risk of developing delirium in patients in general medicine wards. The observed NNT of 13 makes it absolutely applicable with tangible benefits. The application of this kind of intervention seems to be cost- effective and could improve prognosis of hospitalized older patients.					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	Observers not blind to allocation group
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	Observers not blinded to outcome assessment
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Intervention was carried out by family members who could have implemented other measures that may have influenced delirium development
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 5**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G3-G5-Rubin FH, Williams JT, Lescisin DA, et al. Replicating the Hospital Elder Life Program in a community hospital and demonstrating effectiveness using quality improvement methodology. J Am Geriatr Soc. 2006;54(6):969-74

Study Characteristics	Population	Intervention Groups	Results		Comments
			Measure	Outcome	
RubinFH 2011 USA **Setting** Community teaching hospital **Study Design** Pre-test/post-test quality improvement study **Selection method** Patients admitted to a nursing unit **Study Length/Start-Stop Dates** 2001 - 2002 **Purpose** To evaluate a replication of the Hospital Elder Life Program (HELP), a quality-improvement model, in a community hospital without a research infrastructure, using administrative data **Funding source(s):** Shadyside Hospital Foundation funded the Shadyside replication. The HELP dissemination effort was funded in part by grants from the National Library of Medicine, the Commonwealth Fund the Fan Fox and Leslie R. Samuels Foundation), and the Retirement Research Foundation. **Quality Score**: 3 **Risk of Bias**: High	**N = 1929** n = 1225 baseline (pre-intervention) n = 704 post intervention **Inclusion** Aged ≥ 70 Admitted to Hospital Elder Life **Exclusion** N = not discussed -Diagnosis of schizophrenia -Baseline use of major tranquilizers **HELP Implementation personnel** -Elder life specialist (1.0 FTE) -clinical geriatrician (0.1 FTE) -geriatric nurse practitioner (0.5 FTE)	**n = 704 HELP Intervention** Time period: 7/2002 – 12/2002 Men and women (63.5%) Mean age 80.9 (6.7) Phase in data collected 1/2002 through 6/2002 HELP implementation 7/2002-12/2002 **Protocol** **Hospital Elder Life Program** Daily interventions targeted patients were not delirious and who were at intermediate risk for developing delirium Risk factors present: -cognitive impairment -sleep deprivation -immobility -visual or hearing impairment -dehydration Deviations from the original HELP model -exercise and fluid repletion protocols omitted due to insufficient staffing -sleep protocol modified -the Role of the nurse practitioner was modified to eliminate redundancies with existing services	**Delirium assessment:** Specific assessment tools not described **Baseline characteristics** Cerebrovascular disease Gastrointestinal disease Ischemic heart disease Renal failure **Primary outcomes** Delirium rates **Financial outcomes** Est 101 cases prevented 14.4% reduction in delirium rate Net cost savings (cost savings –cost of HELP) **Nursing satisfaction outcomes** Nurses and nurses' aides Agreed Highly agreed Patient satisfaction with HELP	A nurse practitioner evaluated patients for the presence of delirium and for the presence of modifiable predisposing or precipitating factors. She interacted with staff nurses and treating physiciabns. Significant difference between groups Baseline vs HELP 7.4% vs 3,7%, p .001 5.1% vs 12.4%, p <.001 2.7% vs 4.5%, p .04 0.4% vs 1.4%, p .03 **Baseline vs. Intervention** 40.8% vs. 26.4% p < .002 $220,281 cost savings 364 bed-days saved $562,611 in 6 mos on one 40-bed nursing unit "My job is more satisfying due to HELP" "It would be helpful to make HELP a permanent program on my unit" 2.8/3 rating for overall satisfaction	Factors contributing to success at Shadyside included -a long tradition of QI improvements for elderly inpatients; -inclusion of all stakeholders in the project, especially nursing and ancillary personnel, so that concerns of competition or ''turf'' were resolved at the outset; -an accompanying educational campaign to generate support; -an identified senior physician champion; -use of data that hospital leadership found credible; -agreement with management at the outset on what outcomes would be important; -beginning with only one unit; -institution-wide celebration of results.
		n = 1,225 Baseline (control) Time period: 1/2001 – 12/2001 Men and women (63.8%) Mean age 80.6 (6.2) Baseline data measured throughout 2001 **Protocol** Standard care	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Secondary outcomes**	See above See above See above See above	

Conclusion: **Conclusion**: HELP can be successfully replicated in a community hospital, yielding clinical and financial benefits

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	Individuals not randomized or individual matched. Differences between groups
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	Allocation not concealed due to different time periods
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	Outcome assessors not blinded
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Pre/post design Cohorts were assessed at different time periods and thus there may be other confounding variables
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	0		Delirium assessment tool not described
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 3**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G3-Bjorkelund KB, Hommel A, Thorngren KG, et al. Reducing delirium in elderly patients with hip fracture: a multi-factorial intervention study. Acta Anaesthesiol Scand. 2010;54(6):678-88

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects Comments
			Measure	**Outcome**	
Bjorkelund KB 2010 **Sweden** **Setting** University Hospital **Study Design** Prospective, population-based, quasi experimental study **Selection method** Consecutive patients admitted with hip fracture **Study Length/Start-Stop Dates** 4/2003-4/2004 **Purpose** To investigate whether an implementation of a multi-factorial program, including intensified pre-hospital and perioperative treatment and care could reduce the incidence of delirium in elderly patients with hip fracture and cognitively intact at admission. **Funding source(s):** Swedish National Board of Health and Welfare, the Swedish Association of Local Authorities and Regions, HSF, Council for Medical Health Care Research in Southern Sweden **Quality Score:** 3 **Risk of Bias**: High	**N = 478 assessed for eligibility** n =139 excluded n = 1 denied participation **N = 276 eligible** n = 139 intervention n = 136 control **Inclusion** -Age ≥ 65 -Assessed as cognitively intact at admission -SPMSQ ≥ 8 **Exclusion** N = 139 total n = 35 Age < 65 n = 104 for -SPMSQ < 8 -History of cognitive impairment, -Severe neuropsychiatric illness, -Communication difficulties -Multi-trauma **Cognitive/Delirium Assessment** Short Portable Mental Status Questionnaire (SPMSQ) Organic Brain Syndrome Scale (OBS)	**n = 139 Intervention (admitted after 10/1/2003)** n=8 excluded n=2 no operation n=6 Hx/treatment of previous delirium, dementia **n = 131 analyzed** Men and women (71%) Mean age 81.1 (7.5) **Protocol (initiated 10/1/2003)** Screened for cognitive impairment within 30 min after admission to the ED using the SPMSQ and within 4 h for delirium and daily thereafter using the OBS Other multi-factorial program components: 1. Supplemental oxygen 3-4l/min 2. Intravenous (i.v.) fluid supplementation and extra nutrition 3. Increased monitoring of vital physiological parameters 4. Adequate pain relief 5. Avoid delay in transfer logistics 6. screen for delirium through daily testing with the OBS scale 7. Avoid polypharmacy 8. Standard protocols for -premedication, anesthesia, monitoring, blood loss/transfusion, Sedation, postoperative analgesia	**Delirium assessment:** SPMSQ OBS DSM-IV **Baseline characteristics** Walking ability Use of diuretics S-sodium(m/mol) S-potassium(m/mol) **Delirium outcomes** Delirium during hospitalization Post-operative delirium Developed hypoxia **Significant risk factors** **Age ≥ 80** Institutional care **Need walking aids** **SPMSQ score 8 or** 9 Neurological diagnosis Rx drugs ≥4 Rx diuretics Rx nitroglycerine **Rx anticholinergic** **Cardiac failure** **BOLD** = significant intervention and control	Post-op, patients were tested a minimum of 8h after the end of anesthesia and daily by 2 researchers. Patients showing signs of delirium when tested with the OBS scale or were reported as delirious by the nurse were evaluated in relation to the DSM-IV criteria of delirium on a later occasion by a psycho-geriatrician Significant differences: **Intervention vs. Control** 84% vs. 93.9% p=.036 31.3% vs. 47% p=.009 142(139-144) vs.141(138-143) p=.047 3.8(3.6-4.1) vs. 4 (3.7-4.3) p=.013 **Intervention vs control** 22.1% vs. 34.1% p=.031 21.4% vs. 33.3% p=.030 9.8% vs. 20% p=.026 **Delirium % vs no delirium %, p** **89.7% vs 48.0% <0.0001** 31,.0% vs 7.8%, 0.003 **69.0% vs 38.2%, 0.003** **86.2% vs 33.3%, <0.0001** 37.9% vs 17.6% 0.020 79.3% vs 51.5%, 0.008 51.7% vs 25/5%, 0.007 20.7% vs 2.9%, 0.004 **58.6% vs 22.5%, <0.0001** **13.8% vs 2.9%, 0.042**	**Adverse effects** No significant difference between groups other than delirium Differences in pre- intra- and post-operative data (see data Table 4) *Significant differences* -SpO2 preop, <0.0001 -SpO2 Day 2, <0.0001 -heart rate lowest, 0.043 -Body temp, 0.004 -i.v. fluid preop, <0.0001 -i.v. fluid postop, 0.001 -analgesics RR, 0.009 -antiemetics (anesthetic period), <0.0001 -admission Orth ward preop, <0.0001 Limitations -use of quasi-experimental design -unable to change the way patients were located in the hospital (admitted to available bed) -no blinding of clinical personnel who had to be trained to deliver the protocols -presence of pain or tx with opioids may have influenced initial SPMSQ score and affected exclusion of some patients -researchers not blinded to the use of the OBS which may have influence the reliability of the assessments
		n = 136 Control (admitted before 10/1/2003) n = 4 excluded n = 1 no operation n = 3 Hx/treatment of previous delirium, dementia Men and women (69.7%) Mean age 82(7.6) **Protocol** Usual care	**Delirium assessment:** **Significant risk factors** Female Male **Age ≥ 80** Impaired hearing **Need walking aids** **SPMSQ score 8 or 9** ASA III + IV **Rx anticholinergic** S-hemoglobin <6.2 (mmol/l S-potassium >4.7 (mmol/l)) S creatinine >100 (µmol/l) Blood transfusion <2U **Cardiac failure** Myocardial infarction Death within 30 days of surgery	Not described **Delirium % vs no delirium %, p** 55.6% vs 77.0%, 0.011 44.4% vs 23.0%, 0.011 **88.95 vs 51.7% <0.0001** 64.4% vs 32.2%, <0.0001 **66.7% vs 41.4%, 0.006** **75.6% vs 28.7%, <0.0001** 51.1% vs 24.1%, 0.002 **48.9% vs 29.9%, 0.031** 13.3% vs 1.1%), 0.006 11.4% vs 2.4%, 0.045 33.3% vs 13.8%, 0.008 75.6% vs 93.0%, 0.005 **17.8% vs 3.4%, 0.008** 11.1% vs 0, 0.004 8.9% vs 0, 0.012	
Conclusion: The use of a multi-factorial intervention program based on early and intensified care and supporting treatment in elderly hip fracture patients, lucid at admission, reduced the incidence of delirium during hospitalization from 34% to 22%.					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	. Significant differences between groups at baseline
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	Quasi-experimental design (before/ after implementation of intervention program)
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	Study design – no blinding
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	Unclear	Exclusions/dropouts after group assignment (<10%)
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Problematic study design (historical controls; before/after study) Baseline imbalances Possible confounders
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 3**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G3-Vidan MT, Sanchez E, Alonso M, et al. An intervention integrated into daily clinical practice reduces the incidence of delirium during hospitalization in elderly patients. J Am Geriatr Soc. 2009;57(11):2029-36

Study Characteristics	Population	Intervention Groups	Results		Comments
			Measure	**Outcome**	
Vidan MT 2009 **Spain** **Setting** University Hospital **Study Design** Controlled clinical trial **Selection method** Consecutive patients admitted to geriatric acute unit and internal medicine wards **Study Length/Start-Stop Dates** 1/2007-12/2007 **Purpose** To analyze the effectiveness of a multicomponent intervention integrated into daily practice for the prevention of in-hospital delirium in elderly patients **Funding source(s):** Grant from Spanish Geriatrics Society, Public Grant from Fondo de Investigacion Sanitaria-Instituto de Salud Carlos II **Quality Score** 4 **Risk of Bias**: Unclear	**N = 1,027 eligible** n = 904 screened n= 362 excluded (most because of severe dementia) -140 excluded intervention group -222 excluded control group **N = 542 included and analyzed** **Inclusion** Age ≥ 70 -Admitted to geriatric acute care unit -Admitted to two internal medicine wards -Had at least one of four risk factors of delirium - cognitive impairment, - visual impairment, -acute disease severity -dehydration) **Exclusion** **N = 362** -Delirium at time of admission -Presence of severe dementia that impaired communication -Aphasia of any origin -Coma -Agnoic status -expected hospital LOS < 48 h **Assessments** CAM ADLs Functional Ambulation Classification (mobility) APACHE II Charlson Comorbidity Index MMSE	**n = 170 Intervention (geriatric unit)** Men and women (62.4%) Mean age 85.9 (6) **Protocol** -Quality improvement program with two major components: 1. An educational program aimed at changing the approach of geriatric ward staff to patient care 2. A set of specific targeted actions in seven risk factor domains Started in the first 24 h of admission as part of standard clinical practice by all clinical staff The specialist geriatric nurse coordinated nursing interventions. Most actions were performed daily in all patients, and others, such as interventions involving hydration and nutrition, were performed only if necessary. Adherence was monitored using a checklist of actions evaluated every day for each member of the sample.	**Delirium assessment:** CAM **Baseline characteristics** Age Female Widowed Living at home before admission # basic ADLS performed any impairment in ADLS independent ambulation mean MMSE score Hearing impairment High risk of delirium **Primary outcomes** Incidence of delirium Mean intensity of delirium (0-7) Length of delirium episode (h) Patients with >1 episode (n) Functional decline in delirium patients Intermediate risk for delirium Mortality Functional decline Subgroup analysis matched for age and risk factor Logistic regression for significant risk factors Dementia Baseline ADL independence In hospital stay (per day) Intervention group	A trained RA tested each delirium criterion daily (every morning) in all patients using a structured interview. To detect delirium episodes in the afternoon and evening or at night, a family member and the attending nurse were interviewed daily, and the medical records were reviewed. **Intervention vs. Control** 85.9 vs. 82.1 p<.001 62.4% vs. 53% p=.04 64.7% vs. 51.8% p=.01 77.2% vs. 85.7% p=.01 3,28(2.1) vs. 3.8(1.9) p=.02 78.8% vs. 73.4% p=.04 35% vs. 51% p=.001 20.8(6.7) vs. 21.8(6.5) p=.04 64% vs. 45.9% p=.001 44% vs. 29% p=.001 11.7% vs. 18.5% p=.045 No significant difference 4.9 (0.4) vs 5,3 (1,.0), p=.08 32.1 (43.0) vs 33.6 (22.0), p=.73 0/20 vs 6/69, p=.22 60% vs 71.2%, p=.41 6.3% vs 15.2%. p=.03 2/20 vs 10/69, p=.60 45.5% vs. 56.3% p =.03 Delirium incidence = 11.3% vs. 21% p=.01 2.14 (1.15-3.99), p=.02 0.78 (0.69-0.89), p=.001 1.02 (1.00-1.05), p=.05 0.43 (0.24-0.77), p=.005	Adherence Overall rate of adherence was 75.7% of patient-days per intervention actions, with the highest rate in mobilization (91%) and the lowest in sleep preservation (50%). The intervention was also successful at improving other parameters that can be considered quality indicators in the management of elderly hospitalized patients. The use of glasses and hearing aids increased in patients who needed them, as did the rates of daily mobilization, and the use of physical restraints was reduced. In addition, the intervention increased the number of patients taking daily mobilization exercises and reduced the rate of functional decline without an increase in the incidence of falls during hospitalization, suggesting that the program is safe.
		n = 372 Control (internal medicine units) Men and women (53%) Mean age 82.1 (6) **Protocol** Usual care	**Delirium assessment:** **Baseline characteristics** **Primary outcomes**	See above See above See above	
Conclusion: The incidence of delirium during hospitalization in elderly patients can be reduced with an intervention protocol aimed at reducing the number of precipitating factors and improving the quality of care. This intervention can be completely integrated into daily clinical practice.					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	Many baseline significant differences between groups
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	Unclear	Patients assigned to different wards, but potential for nursing staff to work on both wards
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	Unclear	No blinding, but attempts to conceal allocation
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	Unclear	Used ITT to evaluate intervention effectiveness and baseline characteristics with potential confounding effects included in logistic regression analysis and secondary subgroup analysis using matched controls
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = Unclear**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 4**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G3-G5-Inouye SK, Bogardus ST, Jr., Baker DI, et al. The Hospital Elder Life Program: a model of care to prevent cognitive and functional decline in older hospitalized patients. Hospital Elder Life Program. J Am Geriatr Soc. 2000b;48(12):1697-706

Study Characteristics	Program Personnel	Program Description	Results		Comments
			Measure	Outcome	
Inouye SK 2000 **USA** **Setting** General medicine service at urban university hospital **Study Design** QI Evaluation of HELP implementation **Selection method** NA **Study Length/Start-Stop Dates** 3/1995-8/1999 **Purpose** To describe the Hospital Elder Life Program, a new model of care designed to prevent functional and cognitive decline of older persons during hospitalization. **Funding source(s):** CCT funded by private foundation grants and NIA Yale New Haven Hospital assumed funding for the program as a permanent hospital program in January 1998. **Quality Score** 5 **Risk of Bias**: Unclear	**N = approximately 800 patients/year in 2000 (200-250 patients at start up)** **Program personnel** -Elder Life Nurse Specialist -Elder Life Specialist/ Volunteer Coordinator -Geriatrician -Program Director **Volunteers** -carry out core interventions -rigorous selection criteria -extensive training -didactic and small group -one : one on wards -weekly shift commitments -minimum 6 month program commitment -must meet competency evaluation by Elder Life Specialist before initial patient contact -quarterly competency checks -retention enhanced -staff communication -educational sessions -support groups -monthly newsletter -recognition incentive awards **Interdisciplinary expertise** Consultation and support to the program -geriatric nurse practitioners -geriatric chaplaincy -clinical pharmacy -nutrition -rehabilitation therapies (physical, occupational, recreational) -care coordination -social work **Administration** -HELP Working Group -Program Director/ Geriatrician -nurse specialists -Elder Life specialists -Community Advisory Board	**Enrollment criteria** **Inclusion** Age ≥70 ≥1 risk factor for cognitive or functional decline -MMSE ≤24 -mobility or ADL impairment -Dehydration -Vision impairment -Hearing impairment Able to communicate verbally or in writing **Exclusion** Coma Mechanical ventilation Aphasia Combative/dangerous behavior Severe psychotic disorder Severe dementia (case by case) Respiratory isolation Discharge within 48 hours Refusal by patient, family, physician Other (documented) **HELP Intervention** Goals: (1) to maintain physical and cognitive functioning throughout hospitalization; (2) to maximize independence at discharge; (3) to assist with the transition from hospital to home; and (4) to prevent unplanned readmission. **Core interventions** Carried out by program staff and volunteers -protocols for daily visitor/ orientation -therapeutic activities -early mobilization -vision/ hearing -oral volume repletion -feeding assistance, -sleep enhancement. -geriatric nursing assessment and intervention -interdisciplinary rounds -provider education program -community linkages and telephone follow-up -geriatrician consultation -interdisciplinary consultation	**Quality assurance procedures** *Adherence* (overall rates for all interventions) *Non adherence* Staff/volunteers not available Patient refusal Medical contraindication Patient unavailability **Program benefits** MMSE ADL **Ongoing HELP Outcomes** Median LOS Discharged to home Discharged to short-term rehabilitation in nursing home **Sleep Protocol Effectiveness** Protocol adherence Reduction in sedative use **Other Program Benefits** Reduced overall hospital costs Community perception of high quality geriatric care Geriatric education/expertise resource **Program Costs** Equipment and supplies Average daily census Intervention visits/day Staff effort Minimum volunteers Consultants	**Adherence rates:** 89% for 37,131 patient-days 32% 26% 22% 13% **Intervention vs control** 8% decline in MMSE 2+ points vs. 26% in controls (proportionate increment=0.69) 14% decline in ADL 2+ points vs. 33% in controls (proportionate increment=0.58) 7 days (1-163 d) 56% 15% 74% adherence; no adv effects 54% vs. 31% (p< .02) 200-256 patients/year $3,000 (startup) for 1-2 units 4-5 patients 12-15 (per 3xday protocols) 1.6 to 1.7 FTEs 21 (1 shift/week)' 6 patients/shift Costs not included in program budget	The HELP program is unique in its hospital-wide focus, provides skilled staff, including trained volunteers, to provide interventions to all patients. A dedicated geriatric unit is not required A unique strength of the program is the targeting of common, modifiable, evidence-based risk factors that are relevant to older hospitalized patients using interventions to be feasible and generalizable to other settings. Effectiveness of the program has been demonstrated through research studies for prevention of delirium and cognitive and functional decline. The HELP program is readily adaptable to other hospital settings. Barriers to implementation in other settings -institutional support for start up personnel and equipment -changing ingrained geriatric practices -developing support from key nursing and physician personnel -ongoing clinical personnel training -frequent turnover of personnel -recruitment (extensive) training and retention of volunteers
Conclusion: These results suggest that the Hospital Elder Life Program successfully prevents cognitive and functional decline in at-risk older patients. The program is unique in its hospital-wide focus; in providing skilled staff and volunteers to implement interventions; and in targeting practical interventions toward evidence-based risk factors. Future studies are needed to evaluate cost-effectiveness and long- term outcomes of the program as well as its effectiveness in non-hospital settings.					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	Unclear	Not applicable
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	Unclear	Not applicable
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	1	Low	
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	Unclear	Non-concurrent controls from prior RCT
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = Unclear**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 5**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G3-G5-Lundstrom M, Olofsson B, Stenvall M, et al. Postoperative delirium in old patients with femoral neck fracture: a randomized intervention study. Aging Clin Exp Res. 2007;19(3):178-86.

Study Characteristics	Population	Intervention Groups	Results		Comments
			Measure	Outcome	
Lundstrom M 2007 **Sweden** **Setting** University hospital **Study Design** RCT **Randomization method** Sealed envelope. Stratified according to dislocation of fracture. **Study Length/Start-Stop Dates** 5/2000 – 12/2002 **Purpose** To determine whether a postoperative multi-factorial intervention program, including comprehensive geriatric assessment, management and rehabilitation, can reduce delirium and improve outcome in patients with femoral neck fractures. **Funding source(s):** Vardal Foundation, Joint Committee of the Northern Health Region of Sweden , JC Kempe Memorial Foundation, Foundation of the Medical Faculty, University of Umeå, County Council of Västerbotten and Swedish Research Council, Grant **Quality Score:** 6 **Risk of Bias**: High	**N = 353 patients assessed for eligibility** n = 154 excluded **N = 199 randomized and analyzed** **Inclusion** -Age ≥ 70 -Consecutively admitted to Orthopedic Department -Femoral neck fracture **Exclusion** N = 154 n = 95 did not meet inclusion criteria n= 11 Refused to participate n=27 missing due to failed inclusion routines n = 21 suffered fracture in hospital -severe rheumatoid arthritis -severe hip osteoarthritis -severe renal failure -pathological fracture -patients who were bedridden before fracture due to the operation methods that were planned to be used in the study Other assessments Geriatric Depression Scale (GDS) Prefracture Personal ADLs (P-ADL)	**n = 102 Intervention** n = 6 patients died during hospitalization n = 92 assessed at 4 months n = 86 assessed at 12 months Men and women (72.5%) Mean age 82.3 (6.6) **Protocol** -Patients randomized to the intervention group were admitted to a 24-bed geriatric unit specializing in geriatric orthopedic patients. -The staff applied comprehensive geriatric assessment, management and rehabilitation **Main content of intervention protocol** -Staff education -Teamwork -Individual care planning -Delirium prevention, detection, treatment -Prevention/treatment of complications -infection -anemia -embolism -Bowel/bladder function	**Delirium assessment:** MMSE Organic Brain Syndrome Scale (OBS) DSM – IV **Baseline characteristics** Depression Antidepressants **Primary outcomes** Days postoperative delirium Patients delirious postop Significant difference between groups for each day (1-7) Delirious after the seventh postoperative day Delirious at discharge **Secondary outcomes** Urinary infections Sleeping problems Falls Decubitus ulcers Assessments of underlying causes of delirium documented in medical records Length of Stay (LOS) (days) LOS for patients with postop delirium LOS for delirium patients with dementia Dementia patients with postop delirium at discharge	Delirium assessments by study nurses daily postop days 1-7; blinded specialist in geriatric medicine analyzed all assessments and documentation once during hospitalization No significant differences, except: **Intervention vs. Control** 32.4% vs. 47.4%, p 0.031 28.4% vs.46.4%, p 0.009 **Intervention vs. Control** 5.0 (7.1) vs. 10.2(13.3) p =0.009 54.9% vs. 75.3% p=0.003 p =0.001 18% vs. 52% p< 0.001 0 vs. 20 patients p < 0.001 **Intervention vs. Control** 39.3% vs. 60.3% p =0.018 28.6% vs. 50.7% p = 0.011 17.9% vs. 34.3% p = 0.034 10.7% vs. 23.6% p=0.059 2.28(1.25) vs. 0.90(0.90) p<.001 28(17.9) vs. 38(40.6) p= 0.028 31.4(19.3) vs. 43.6 (42.7) p= 0.032 3.2 (4.1) vs 12.8 (17.6), p = 0.003 0 vs 15, p <0.001	**Multivariate linear regression to control for baseline differences** **Dependent variable = number of days with postop delirium** **Independent variables (p)** -delirium post op (<0.001) -control group (0.001) -male sex (0.004) -depression (NS) -dementia (NS) -age (NS) Despite some baseline differences between the intervention and control groups, there was still a strong association between number of days with postoperative delirium and being treated in the control group. The effect of the intervention program seemed to reduce the incidence of delirium on the first postoperative day. This may be explained by the fact that, when the patients arrived at the intervention ward, they were immediately and systematically assessed to detect, treat and prevent any complications that would cause delirium. Patients with dementia seemed to have benefited from the intervention program. All parts of the intervention program, which are probably equally important should be systematically adapted with focus of detection, prevention and treatment of delirium Limitation -psychiatric symptoms and cognitive testing only 1 time during hospitalization
		n = 97 control Men and women (76.28%) Mean age 82 (5.6) **Protocol** Usual postoperative care in the orthopedic department Patients needing further in-hospital rehabilitation (n = 40) admitted to a geriatric ward but not the intervention ward	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Secondary outcomes** **Delirious control patients received** More sedatives More opioid drugs on demand	See above See above See above See above 41.7% *vs* 15.4%, p=0.008 61.7% *vs* 30.8%, *p*=0.004	
Conclusion: This study shows that postoperative delirium can be successfully treated by a team applying comprehensive geriatric assessment, management and rehabilitation. The intervention program resulted in fewer days with delirium, fewer other complications, and shorter hospital stays. Implementing this intervention program will probably have a great humanitarian and economic impact, and is probably applicable to surgery on old people in general. Therefore, the organization of surgical wards should be reconsidered and adapted to the needs of the oldest and frailest patients.					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	Significant differences in baseline characteristics
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	No blinding during outcome assessment (record reviews)
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	1	Low	
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 6**

Instructions on rating:

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  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G-3 Chen CC, Lin MT, Tien YW, et al. Modified hospital elder life program: effects on abdominal surgery patients. J Am Coll Surg. 2011;213(2):245-52.

Study Characteristics	Population	Intervention Groups	Results		Comments
			Measure	Outcome	
Chen 2011 **Taiwan** **Setting** Gastrointestinal ward of an urban medical center **Study Design** Pre/post comparison; clinical trial **Selection method:** **C**onsecutive patients who underwent elective abdominal surgery procedures; allocation by date of admission **Study Length/Start-Stop Dates** 8/2007-4/2009 **Purpose** To examine the effects of a modified Hospital Elder Life Program (HELP) intervention in reducing functional decline of older patients during hospitalization for abdominal surgery. **Funding source(s):** -Taiwan National Science Council grant -Retirement Research Foundation grant -Career development grant from the National Health Research Institute **Quality Score** 4 **Risk of Bias**: High	**N = 217 eligible patients** N = 28 declined participation n = 6 "not feeling well" n = 4 family members declined n = 18 did not consent **N = 189 enrolled** **N = 10 not in analysis** n = 7 died n = 3 withdrew consent **Comparison groups** **N = 179** **n = 102 intervention** **n = 77 control** **Inclusion** Age ≥ 65 -Admitted to gastrointestinal ward -Scheduled for elective abdominal surgery -Expected LOS longer than 6 days **Exclusion** N =34 n = 9 with profound sensory impairment or aphasia that precluded verbal communication n = 14 Intubation or respiratory isolation n = 8 Severe dementia, coma, critical condition **Outcome assessment tools** Chinese BI (functional status) Chinese Mini-Nutritional Assessment (MNA) Chinese Geriatric Depression Scale Short Form (GDS-15)	**n = 102 HELP intervention** (enrolled May 2008 to April 2009) Mean Age 73.3(5.4) Men and women (46.1%) **Modified HELP Protocol** Implemented by full-time trained HELP nurse blinded to the study outcomes, who was not an outcomes assessor. The same attending physicians provided clinical care to both groups Daily hospital-based care including 3 key protocols: 1) early mobilization -ambulation or active range-of-motion exercise 3 times daily 2) nutritional assistance -daily oral care involving tooth brushing, nutrition screening, diet education, and feeding assistance if needed 3) -therapeutic (cognitive) activities -orientating communication and cognitively stimulating activities, such as discussing current events or word games 3 times daily) All 3 protocols implemented as soon as patents returned to surgical inpatient ward and ended at hospital discharge 54% of intervention group received approximately 7 days of the modified HELP protocol	**Delirium assessment:** CAM MMSE **Baseline characteristics** More periampullary cancer More Whipple procedures performed Longer surgery duration Fewer open procedures Better ADL performance Better nutritional status **Primary outcomes** Incidence of delirium Change from baseline to discharge Better functional status BI Score decline Better nutritional status MNA score decline Better cognitive function MMSE score decline **Secondary outcomes** Fewer depressive symptoms (decline of GDS-15) Reduced body weight Less decline in kg Grip strength Less decline in kg	2 trained/blinded study assistants conducted assessments at admission and hospital discharge; inter-rater reliability and severity not discussed **Significant difference Intervention vs. control** 29.4% vs 15.6% (p = 0.03). 18.6% vs 9.1% (p = 0.05) 226.8 ± 91.1 minutes vs 199.0 ± 68.7 minutes (p =0.04), 73% vs 88.3% , p = 0.01 98.0(6.1) vs. 92.2 (13.6) (p < 0.001) 24.0(3.5) vs. 20.7(4.0) (p < 0.001) **Intervention vs. control** 0 (0%) vs 12 (16%), p <0.001 11.8 vs. 27.9 points; p < 0.001 2.8 vs 7.6 points; (p < 0.001) 0.4 vs 1.4 MMSE points 0.3 vs. 4.4 p<0.001 2.2 vs. 3.1 p=0.002 1.2 vs. 2.6 p<0.001	10 patients lost to attrition were not included in analysis The modified HELP intervention has great potential to be clinically feasible for effectively reducing in-hospital functional decline among older surgical patients. Receiving 7 days of the modified HELP intervention prevented full functional loss in 2 to 3 ADLs (or partial loss in function across more ADLs), decreased weight loss by 30%, and reduced delirium rates before hospital discharge, which are clinically important results. Family caregivers are also present at bedside in Taiwan which may have helped the nurse who was administering HELP interventions Limitations -possible selection bias -temporal separation of study groups (study design) -intervention tested on only one ward -other confounding factors possible
		n = 77 control group (usual care) (admitted 8/2007-4/2008) Mean Age 72.6 (6.1) Men and women (44.2%)	**Delirium assessment** **Baseline characteristics** **Primary and secondary outcomes**	See above See above See above	
Conclusion: The modified HELP intervention was successfully implemented and it ameliorated postsurgical functional decline and delirium rates for older patients undergoing common elective, abdominal surgical procedures.					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	Significant baseline differences between groups
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	NA – allocation by date of admission
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	Only outcome assessors blinded
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	(dropouts 5%)
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Study design (pre/post) Baseline imbalances Possibility of confounding factors such as increased medical attention from trained nurse in HELP
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 4**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G3-Inouye SK, Bogardus ST, Jr., Williams CS, et al. The role of adherence on the effectiveness of nonpharmacologic interventions: evidence from the delirium prevention trial. Arch Intern Med. 2003;163(8):958-64.

Study Characteristics	Population	Intervention	Results		Adverse Effects/ Comments
			Measure	**Outcome**	
Inouye 2003 **USA** **Setting** Medicine service at a university hospital **Study Design** Prospective observational **Selection method** Consecutive patients admitted to one general medicine floor **Study Length/Start-Stop Dates** 3/1995-3/1998 **Purpose** To examine the impact of level of adherence on effectiveness of the intervention strategy in a large clinical trial of nonpharmacologic interventions to prevent delirium **Funding source(s):** Grant from NIA and in-kind support from Claude D. Pepper Older Americans Independence Center given by the NIA **Quality Score**: 6 **Risk of Bias**: Unclear	**N = 871 met inclusion criteria** **n = 422 final study sample** Men and women (60.9%) Mean age 79.7 (6.11) MMSE = 23.7(4.57) MMSE <24 = 41% Modified Blessed DRS 1.6(2.17) Baseline delirium risk --Intermediate 72% --High 28% **Inclusion** Age ≥ 70 -no delirium at admission -at least intermediate risk of delirium at baseline **Exclusion** N = 335 n=117 inability to participate in interviews for reasons such as profound aphasia or intubation n=34 coma or terminal illness n=89 hospital stay of less than 48 hours n=95 unavailability of interviewer or patient n=114 refusals by patients, families, or physicians Excluded patients did not differ significantly from enrolled patients in terms of age, sex, or baseline delirium risk	**N = 422** **Protocol** -implemented by Elder Life Specialists (trained hospital staff members) and assisted by trained volunteers, -overseen by a geriatric clinical nurse specialist and geriatrician -all patients assigned to receive orientation, mobility, and therapeutic activities protocol, -other protocols were assigned according to risk factors present at screening. -other protocols include sleep, hearing or vision, and volume repletion - patients were reassessed daily for changes in risk factors that might necessitate changes in their protocol assignments -staff and volunteers underwent quarterly standardization with completion of competency-based checklists for consistency -level of adherence recorded daily as full or partial	**Delirium assessment:** MMSE CAM **Baseline characteristics** **Primary outcomes** Overall rate of complete adherence with all intervention protocols Combined partial and complete adherence Adherence rate by intervention protocol across all patient-days Orientation Mobility Therapeutic activities Sleep Vision-hearing Volume repletion **Adherence Group** Low Intermediate High p-value Significant decrease in incidence of delirium with higher levels of adherence using composite adherence score (orientation, mobility, and therapeutic activities). Stratified by baseline delirium risk group (intermediate vs. high), the relationship of lower incidence of delirium with higher levels of adherence persisted **Protective Effect of Adherence on Delirium Rate** Unadjusted Adherence Full adjusted adherence	MMSE, CAM measured at baseline within 48 hrs of admission, and daily by separate blind research team members who underwent standardization, and inter-rater reliability assessment 86.7% with impairment of IADLs 34.4% impairment of ADLs High indexes of illness burden -mean APACHE II 15.5 -mean Charlson index 3.1 57% 87% 86% 36% 63% 10% 83% 57% **Delirium Rates by Protocol** *Orientation/Mobility/Therapeutic* 24% / 14% / 12% 13% / 10% / 10% 7% / 3% / 4% <0.001 / .01 /.06 p_{trend} = .002 P_{trend}=.04 for each delirium group OR .67(.54-.83) p<0.001 OR .69 (0.56-0.87) p= 0.001	No adverse events associated with protocols **Most common reasons for non-adherence** in13% of patient days -52% lack of availability of intervention staff members -27% patient refusal -10% lack of availability of patient because of medical procedures -7% severe medical symptoms preventing participation or medical contraindication **Multivariable analysis** Unadjusted model indicated substantial reduction risk of delirium associated with each 1-point increase in adherence score Adjusted model controlled for age, sex, education, Charlson score, depression, impairment in ADLs, illness severity, MMSE, blood urea nitrogen-creatinine ration, and visual impairment In the fully adjusted model, the risk of delirium of a patient in the highest adherence group was 89% lower than the risk in the lowest adherence group. In the highest adherence group, the rate of delirium was less than 3%.
Conclusion: Adherence played an important independent role in the effectiveness of a nonpharmacologic multicomponent intervention strategy. Higher levels of adherence resulted in reduced rates of delirium in a direct graded fashion, with extremely low levels of delirium in the highest adherence group. Thus, adherence must be ensured in nonpharmacologic interventions to optimize 24 effectiveness.					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	Unclear	Single group observational study, but multivariable analysis did not reveal confounding variables; no difference between included/ excluded subjects
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	Unclear	Participants may have been aware of the interventions/protocols they received
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	1	Low	
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	1	Low	
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = Unclear**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 6**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G3-G5-Lundstrom M, Edlund A, Karlsson S, et al. A multifactorial intervention program reduces the duration of delirium, length of hospitalization, and mortality in delirious patients. J Am Geriatr Soc. 2005;53(4):622-8.

Study Characteristics	Population	Intervention Groups	Results		Comments Conclusion
			Measure	**Outcome**	
Lundstrom M 2005 Sweden **Setting** Department of General Internal Medicine, University Hospital **Study Design** Prospective Controlled clinical trial **Selection method** Consecutive admission to 2 wards (intervention ward; control ward) Random allocation from ED based on available bed; readmissions within 3 months of discharge admitted to the same ward as previous treatment **Study Length/Start-Stop Dates** Not described **Purpose** To investigate whether an education program and a reorganization of nursing and medical care improved the outcome for older delirious patients. **Funding source(s):** Joint Committee of theNorthern Health Region of Sweden (Visare Norr), et al **Quality Score** 3 **Risk of Bias**: High	**N = 400** **Inclusion** Age ≥70 Informed consent **Exclusion** N = not described Age <70 Declined participation **Other assessment (all patients):** RA assessed on Days 1, 3, and 7 after admission Organic Brain Syndrome (OBS) Scale, MMSE Katz ADL index Vision testing (admission) Hearing testing (admission)	**n = 200 Intervention group** Men /women% 39.0/61.0 Mean age 79.4 (5.6) 1. A 2-day course for staff on geriatric medicine focusing on assessment, prevention, and treatment of delirium 2. Education concerning caregiver-patient interaction focusing on patients with dementia and delirium 3. Reorganization from a task-allocation care system to a patient-allocation system with individualized care 4. Guidance for nursing staff once a month No blinding	**Delirium assessment:** DSM-IV **Baseline characteristics** Age Male% vs Female % Diabetes mellitus Stroke % Myocardial infarction **Logistic Regression to Control for Baseline Differences** Ward Stroke on admission Sex Age Diabetes mellitus **Primary outcomes** Delirium incidence Delirium prevalence (24h) Delirium incidence (Day3) Delirium incidence (Day7) **Secondary outcomes** Length of stay(days) Return to home/apt *Delirious patients* Return to home/apt Mortality	Three of the authors rate OBS scale and MMSE on days 1,3, and 7, then determined delirium according to DSM-IV criteria (90% inter-rater agreement) (authors blinded to allocation) Significant difference between groups **Intervention vs control** 79,4 (5.6) vs 80,7 (6.2), p=.02 39.0%/ 61.0% vs 49.5%/50.5%, p=.04 42.5% vs 23.5% p<0.001 170% vs 25.0%, p=..05 10% vs 4.5%, p=.03 **Delirious Patients in the Two Wards (N=125; n = 63 vs n = 62))** OR=3.12 (1.43–6.81) OR=1.44 (0.62–3.35) OR=1.35 (0.59–3.05) OR=1.01 (0.95–1.08) OR=0.53 (0.22–1.27) **Day 1 vs Day 3** 123/400 (30.8%) vs 82/400 (20.5%),p <.001 **Intervention vs control** 31.5% vs 31.0%; p=.91 58.7% vs 72.6%; p=.10 30.2% vs 59.7%; p=.001 **Intervention vs control** 9.4 (8.2) vs 13.4 (2.3); p<.001 86.6% vs 82.4%; p=.29 78.3% vs 60%; p=.05 2 (3.2%) vs9 (14.5%); p=.03	Too few patients had dementia in the present study to allow analyses of patients with dementia separately, but no patient with dementia remained delirious on Day 7 in the intervention ward, compared with four patients still delirious on Day 7 in the control ward, which might indicate that delirium in patients with dementia can be successfully treated. Limitations -randomization/allocation dependent on bed availability -RA assessors not blinded -assessments not done daily -discharged patients regarded as not delirious on Day 7 (1 patient assessed as delirious within 24 h of discharge) **Conclusion** This study shows that a multifactorial intervention program reduces the duration of delirium, length of hospital stay, and mortality in delirious patients.
		n = 200 Control group Men/women % 49.5/50.5 Mean age 80.7 (6.2) Usual hospital care organized in a task-allocation care system; -the same caregiver handled particular tasks for all patients, -no clinical caregiver had full responsibility for an individual patient during his or her entire hospitalization. Staff aware that a screening of delirium prevalence was being performed	**Delirium assessment:** **Baseline characteristics/measures** **Primary outcomes** **Secondary outcomes**	See above	

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	Randomization based on bed availability; significant baseline differences between groups
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	Allocation concealed only for authors who determined delirium dx
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	No blinding except authors who determined delirium dx
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	High	No information on number of patients excluded
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	Unclear	Numerous baseline imbalances, but analyzed to determine OR related to delirious patients Unknown confounders possible because delirium assessment not done daily
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 3**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G3-G5-Tabet N, Hudson S, Sweeney V, Sauer J, Bryant C, Macdonald A, et al. An educational intervention can prevent delirium on acute medical wards. Age Ageing. 2005;34(2):152-6.

Study Characteristics	Population	Intervention Groups	Results		Comments
			Measure	Outcome	
Tabet N 2005 **UK** **Setting** Acute admissions wards in inner-city teaching hospital **Study Design** single-blind case control study **Selection method** Admissions to 2 general acute medical units with similar internal physical features, separate nursing and medical teams on the same hospital floor. Admissions based on bed availability. **Study Length/Start-Stop Dates** 12/2001 to 8/2002 **Purpose** To test whether an educational package on the recognition and management of delirium delivered to medical and nursing staff would decrease the point prevalence of delirium among older hospitalized patients **Funding source(s):** Not described (conflict of interest statements = "none") **Quality Score** 4 **Risk of Bias**: High	**N = 250 recruited** n = 122 intervention n = 128 control **Inclusion** All admissions to intervention/ control wards eligible Age ≥70 Understood and spoke English Agreed to participate No recorded symptoms of delirium in medical or nursing notes on admission In hospital >24 h Informed consent **Exclusion** N = not described Patients who did not meet inclusion criteria **Components of education package** General information on delirium -definition -etiology -epidemiology -symptoms -outcomes Prevention -risk factor recognition -active management of treatable risk factors -high vigilance -active early intervention Management -environmental -nursing care -investigations -identifying and treating underlying causes -management of symptoms Non-pharmacological treatment -assess after 48 h -discontinue before discharge	**n = 122 intervention ward** n = 6 patient case notes not located Men and/women (53.28%) Mean age 81.39 **Educational Package** 1) A 1-hour session including a formal presentation and small group discussion 2) Written information and gidelines on ghow to prevent, recognize and manage delirium in older people 3) Regular one-to-one and small group discussions lasting up to an hour during with staff were encouraged to discuss discharged challenging cases they had encountered with the aim of enhancing their learning experience with specific examples Ward staff received no incentives for adopting the intervention	**Delirium assessment:** Delirium Rating Scale (DRS) Abbreviated Mental Test Score (AMTS) **Baseline characteristics** Mean age **Primary outcomes** point prevalence of delirium Recognition of delirium cases	Unblinded research old age psychiatrists carried out assessments during the daytime. Inter-rater reliability not discussed Significant difference between groups **Intervention vs control** 81.39 vs 79.28, p = 0.007 Significant difference between groups 12/122 (9.8%) vs 25/128 (19,.5%) p=0.034 8/12 (66.66%) vs 6/23 (26.09%), p=0.001	Key Points: 1. Delirium is a common disorder among hospitalized older people Established cases are not readily improved by intervention. 2. Increasing doctors' and nurses' awareness of delirium can be achieved through a brief ad inexpensive educational program. 3. The educational program significantly decreases the prevalence of delirium among older inpatients and increases recognition of cases. 4. Such an educational program can be easily rolled out across hospital unity caring for older people.
		n = 128 control ward Men and women (51.56% Mean age 79.28 Usual care No educational package Established practice was maintained throughout	**Delirium assessment:** **Baseline characteristics** **Primary outcomes**	See above See above See above	
Conclusion: This study demonstrated that an inexpensive educational program significantly decreases the point prevalence of delirium. Increasing awareness of delirium among medical and nursing staff seems to be an effective strategy in preventing delirium.					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	Significant difference in mean age between groups
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	Psychiatrists not blind to study group
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	Outcome assessors not blind to study group
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	High	Not described detail s of exclusion Not reported SD
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Baseline imbalance (age) Limited baseline data reported so possible presence of confounding variables Funding not disclosed
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 3**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

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  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G3-Robinson S, Rich C, Weitzel T, et al. Delirium prevention for cognitive, sensory, and mobility impairments. Res Theory Nurs Pract. 2008;22(2):103-13.

Study Characteristics	Population	Study Groups	Results		Comments
			Measure	Outcome	
Robinson 2008 **USA** **Setting** University Hospital, renal unit **Study Design** Matched Pre/post design **Selection method** Convenience sample of patients admitted before and after implementation of the protocols **Study Length/Start-Stop Dates** Not discussed **Purpose** To determine if a delirium prevention protocol targeting the risk factors could prevent delirium in older adults hospitalized on a renal unit. **Funding source(s):** Not discussed **Quality Score**: 3 **Risk of Bias**: High	**N = 160** n = 80 matched pairs **Matching criteria** -age (w/in 5 years), -gender, -presence of dementia -vision impairment -hearing impairment -mobility impairment **Inclusion** Age > 65 -any combination of delirium risk factors -dementia - vision impairment, -hearing impairment - mobility impairment Admission prior to and after implementation of the delirium prevention protocol **Exclusion** Not discussed **Data source** Medical records Instrument = Chart Based Method for the Identification of Delirium	**n = 80 post intervention (admitted to the renal unit after implementation of the protocol)** Men and women (54%) Mean age 78.82 **Protocol** -On admission, patients assessed for risk factors by the registered nurse admitting the patient. -If patient had any of the risk factors, appropriate interventions were implemented to avoid delirium. -Interventions -implemented by trained nursing assistants -Hospital Elder Life Program (HELP) protocols -Geriatric Nursing Protocols for Best Practice (Forman, Mion et al 2003) -implementation of Delirium Prevention Measures by Risk Factor (Table 1 in PDF) - Clinical nurse III or nurse manager monitored implementation of protocols daily **Nursing Assistant Training** -4 half day classes -delirium -dementia -sensory losses -mobility Nursing staff also trained during staff meetings	**Delirium assessment:** Use of CAM and other data extracted using the Chart-Based Method for the Identification of Delirium **Baseline characteristics** **Risk factors present** 1 risk factor 2 risk factors 3 risk factors 4 risk factors Dementia Vision impaired Hearing impaired Mobility impaired **Primary outcomes** Demonstrated symptoms of delirium at admission Developed delirium on hospital day 2 Patients with dementia and other risk factors Developed delirium (n)	Chart review of medical records to extract data; investigators determined the chart based method was suitable for evaluating broad based clinical programs but not for diagnostic purposes in patient care No significant differences between groups in baseline characteristics or risk factors **All patients (each group, n)** 39 28 11 2 12 (15%) 34 (42.5%) 29 (36.3%) 58 (72.5%) **Pre n (%) vs. Post n (%)** (30) 37.5% vs. (11)13.8% p < .001 28 (93%) vs. (9) 82% N = 12 (all patients) **Pre vs post** 6 vs 1	Eleven of the 80 participants in the post intervention group became delirious, despite implementation of the protocol. Nursing staff continued to use the protocol for these patients to minimize the effects of the delirium. Many of these patients suffered from renal failure. Fluid and electrolyte disturbances were common and may have contributed to the delirium. Limitations -identification of delirium via chart review -CAM was not consistently used pre or post intervention -other risk factor identification were not formally assessed using recognized instruments -the relationship of the prevention protocol to each risk factor could not be examined -the nurses monitoring the protocol implementation did not record the number of times the protocol was not implemented -data on duration of delirium and the presence of delirium at discharge were not recorded
		n = 80 pre intervention (control) Men and women (54%) Mean age 79.18 **Protocol** Usual care	**Delirium assessment:** **Baseline characteristics** **Primary outcomes**	See above See above See above	

Conclusion: The findings of this study indicate that simple interventions targeting dementia, vision loss, hearing loss, and mobility limitations can prevent delirium in some patients when these risk factors are identified and targeted by nurses. Although the protocol prevented some cases of delirium, nursing protocols will not prevent delirium in all elderly patients. A significant reduction in delirium, from 37.5% before protocol implementation to 13.8% after implementation, occurred in the elders receiving the protocol.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	Matched pairs
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	NA – Pre/post design
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	NA – Pre/post design
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	0	High	Due to study design, there was insufficient data to report on important outcomes (see limitations)
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Pre/post design; historical cohorts Risk factors were not assessed with valid instruments Likely that confounders were present and not controlled (even in the presence of matching the cohorts) Funding not described
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	0		Chart review did not include consistent validated assessment
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 3**

Instructions on rating:

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  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G5-Heymann A, Radtke F, Schiemann A, et al. Delayed treatment of delirium increases mortality rate in intensive care unit patients. J Int Med Res. 2010;38(5):1584-95.

Study Characteristics	Population	Study Groups	Results		Comments
			Measure	Outcome	
Heymann A 2010 **Germany** **Setting** University Hospital ICU **Study Design** Prospective observational **Selection method** Consecutive admissions to ICU meeting inclusion criteria **Study Length/Start-Stop Dates** 8/2006 – 11/2006 2/2007 – 5/2007 **Purpose** To clarify the effect of a delay in receiving delirium-specific therapy on patients outcome. **Funding source(s):** Not described **Quality Score** 2 **Risk of Bias**: High	**N = 2640 patients screened** n = 2222 excluded **N = 418 patients analyzed** n = 214 DDS <7 **N = 204 DDS ≥7** n = 184 immediate therapy n = 20 delayed therapy **All patients delirium incidence** 48.8% **All delirium patients**: Median age 63 (18-95) Men and women (33.85) **Inclusion** Age ≥18 Admission to ICU -postoperative -postoperative complications -respiratory failure ICU LOS >72 hours Informed consent **Exclusion** N = 2222 n = 27 age <18 n = 1934 LOS <72 hours n = no evaluation possible or missing values n = 214 DDS <7 Moribund Coma Severe neurological impairment (brain injury) **Assessment tools** Richmond Agitation Sedation Scale (RASS) Delirium Detection Score (DDS) Acute Physiologic and Chronic Health Evaluation II (APACHE II) Simplified Organ Failure Assessment (SOFA) Therapeutic Intervention Scoring System (TISS-28)	**n = 184 immediate therapy (initiated within 24 h after delirium dx)** Men and women (33%) Mean age 62.5 (18-95) APACHE II score 20.2 (5-38) SOFA score 5.7 (0-14) TISS-28 score 33.3 (11-62) Therapy protocol Level of sedation evaluated every 8 h (RASS) RASS ≥ -2: DDS administered DDS administered 3 consecutive days DDS >7 = delirium Standard delirium treatment protocol initiated -medications administered according to protocol	**Delirium assessment:** DDS **Baseline characteristics** Admission APACHE II Admission SOFA Admission TISS-28 Gender Admission APACHE II **Primary outcomes (delirium)** Recurrent delirium episodes Severity at delirium dx Reduction in DDS Correlation time of theray onset with rate of DDS reduction Hypoactive delirium DDS on last day in ICU for immediate therapy group DDS on last day in ICU for delayed therapy group **Other clinical outcomes** Mortality Risk Significant for age Nosocomial infections Pneumonia APACHE II at discharge SOFA score at discharge TISS-28 score at discharge No significant difference between groups	Administered on 3 consecutive days (includes severity; inter-rater reliability not discussed) **Significant difference between groups** **Delirium (204) vs No Delirium (214)** p <0.001 (detail not provided) p <0.001 (detail not provided) p <0.001 (detail not provided) **All delirium patients N = 204** Male 66.2% vs Female 33.8%, p = 0.001 **Immediate (184) vs delayed (20)** 20.2 (5-38) vs 24.7 (18-36), p = 0.005 **Significant difference between groups** **Immediate (184) vs delayed (20)** 2.2 (1.6) vs 2.9 (1.7), p = 0.036 13.9 (5.6) vs 10.2 (3.3), p = 0.001 Greater in immediate (p = 0.004) detail not provided p = 0.014 (See Figure 2) 14% vs 40%, p = 0.041 **Last day vs first day** 5.5 (5.7) vs 13.9 (5.6), p <0.001 7.3 (4,9) vs 10.2 (3.3), NS **Significant difference between groups** **Immediate (184) vs delayed (20)** 16 (8.7%) vs 7 (35%), p = 0.003 HR 3.023 (1.056-8.656) HR 1.035 (1.002-1.070), p = 0.038 134 (72.8%) vs 19 (95.0%), p = 0.029 92 (50%) vs 16 (80.0%), p = 0.017 HR 1.850 (1.023-3.343), p = 0.042 16.9 (6-43) vs 24.1 (7-45), p = 0.002 3.9 (0-18) vs 7.5 (1-19), p = 0.005 27.3 (3-66) vs 36.9 (13060) p = 0.001 Mechanical ventilation days ICU LOS	Important results -a delay in starting delirium therapy was associated with an elevated mortality risk -all ICU scores decreased significantly during the course of the ICU stay in the immediate therapy group but not in the delayed therapy group -this finding supports the idea that a delay in therapy for delirium leads to aggravation of illness and that delirium is not improved when delayed treatment starts. -although the DSS initial score was lower in the delayed therapy group, the immediate therapy group had better delirium and other outcomes Limitations -the number of patients analyzed in each group was small -DDS cutoff of 7 probably did not detect all types of delirium (due to low sensitivity of DDS score) -fewer patients in the delayed therapy group received neuroleptic treatment (35% vs 78%, p not included) which may have influence outcomess
		n = 20 delayed therapy (initiated >24 h after delirium dx) Men and women (45%%) Mean age 69.4 (42-90) APACHE II score 24.7 (18-36) SOFA score 7.1 (3-18) TISS-28 score 36.7 (19-57) Therapy protocol (as above)	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Secondary outcomes**	See above See above See above See above	

Conclusion: An early start to therapy is essential in the treatment of delirium in critically ill patients. Treatment delays may increase the mortality rate, whereas early treatment may decrease progression to multiorgan failure. Sustainable implementation of delirium monitoring is a potentially important aid in the provision of early diagnosis and treatment.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	Many significant differences between all patients and/or study groups
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	NA – observational study
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	NA – observational study
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	0	High	Detailed information not provided for some outcomes; authors note difference in use of neuroleptics may have influenced outcomes (not analyzed)
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Significant baseline imbalances Possibility of confounders (neuroleptic use or study group imbalances) Funding not disclosed
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	0		Delayed n <50
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 2**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G3-G5-Milisen K, Foreman MD, Abraham IL, et al. A nurse-led interdisciplinary intervention program for delirium in elderly hip-fracture patients. J Am Geriatr Soc. 2001;49(5):523-32.

Study Characteristics	Population	Intervention Groups	Results		Comments
			Measure	**Outcome**	
Milisen K 2001 **Belgium** **Setting** Urban academic medical center **Study Design** Prospective longitudinal (pre/post design) **Selection method** Patients admitted to ER with traumatic fracture of proximal femur **Study Length/Start-Stop Dates** 9/1996 - 3/1997 9/1997 - 3/1998 **Purpose** To develop and test the effect of a nurse-led interdisciplinary intervention program for delirium on the incidence and course (severity and duration) of delirium, cognitive functioning, functional rehabilitation, mortality, and length of stay in older hip-fracture patients. **Funding source(s):** The Ministry of Public Health and Environment of the Belgian Government **Quality Score** 4 **Risk of Bias**: High	**N = 120 patients analyzed** n = 60 pre-intervention n = 60 post-intervention **Inclusion** -Patients admitted to the ER w/ traumatic fracture of proximal femur (intra-and extracapsular) -Hospitalized in one of two traumatological nursing units w/in 24 h of surgery -Spoke Dutch and verbally testable **Exclusion** -Multiple trauma concussion of the brain -Pathological fractures, surgery occurring more than 72 hours after admission, aphasia, -blindness -Deafness -Fewer than 9 years of formal education	**n = 60 intervention cohort** (9/1997 – 3/1998) Men and women (81.7%) Median age 82 (13) **Overview** -A system of enhanced quality of nursing care for older hip- fracture patients was developed, implemented, and tested. -Nurses identified high-risk patients and provided prompt anti-delirium interventions to reduce and treat delirium. -Access to readily available consultants and were able to administer regularly scheduled pain medications. Protocol components 1. Education of nursing staff 2. Systematic cognitive screening 3. Consultative services by -delirium resource nurse -geriatric nurse specialist -psycho-geriatrician 4. Use of a scheduled pain protocol	**Delirium assessment:** CAM MMSE **Baseline characteristics** Cardiac comorbidity Vascular comorbidity Abdominal comorbidity **Primary outcomes** Incidence of delirium, n% Duration of delirium (days) Severity of delirium *Mean total CAM scores* Intervention group range Control group range Linear mixed model analysis Cognitive function Sub-dimension memory Memory improvement over time Intervention effect on memory Overall cognitive functioning improved	Trained research nurses obtained information about cognitive functioning (CAM and MMSE) on the first, third, fifth, eighth, and twelfth postoperative days. Significant differences : **Intervention vs. Control** 13.3% vs. 30% p=.045 5% vs. 25% p=.004 5% vs. 20% p=.025 **Intervention vs. Control** 12 (20.0%) vs 14 (23.3%) (p = 0.82 – NS) 1 (1) vs. 4 (5.5), p=.03 **Delirium vs no delirium** 3.82 (2.8) to 1.91 (2.3) vs 0.98 (1.6) to0.87 (1.7) 6.92 (2.8) to 5.0 (3,.1) vs 1.35 (2,.3) to 0.76 (1.4) p = 0.0152, intervention vs control No significant difference in change over time Significant difference in decrease in CAM scores over time (less severity) in both cohorts (p = 0.0013) On average the CAM scores decreased by 0.082 units a day **Intervention vs control** p = 0.0357 (see figure 4) **Delirium vs no delirium** p = 0.0001 (both cohorts) p = 0.0087 both cohorts **Delirium vs no delirium** p = 0.0001 and p 0.0026	There was neither a statistical nor clinical effect for the intervention relative to functional status. There was no significant difference in functional status between the intervention and control cohorts or for either the delirious or nondelirious patients. However delirious patients in both cohorts were more dependent after discharge and 3 months after discharge. Neither cohort of the delirious patients regained their pre-fracture functional status. Delirious patients in both cohorts also had a slower functional rehabilitation over time. There was no significant difference in length of stay between intervention and control groups or between delirious and nondelirious patients Limitations -pre/post study design -less control of confounding variables -use of medical records to obtain historical data This study demonstrated the beneficial effects of an intervention program focusing on early recognition and treatment of delirium in older hip-fracture patients, with the delirious patients in the intervention cohort showing less severe delirium, shorter duration of delirium, and fewer memory problems.
		n = 60 pre-intervention cohort (control) (9/1996-3/1997) Men and women (80%) Median age 80 (12) **Protocol** Usual care	**Delirium assessment:** **Primary outcomes**	See above See above	

Conclusion: This study demonstrated the beneficial effects of an intervention program focusing on early recognition and treatment of delirium in older hip fracture patients and confirms the reversibility of the syndrome in view of the deliriums duration and severity.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	Significant differences in baseline characteristics
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	Pre/post design - no blinding
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	Pre/post design – no blinding
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Pre/post study with historical controls Baseline imbalances Possibility of confounding variables
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 4**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G5-Pitkala KH, Laurila JV, Strandberg TE, Tilvis RS**.** Multicomponent geriatric intervention for elderly inpatients with delirium: a randomized, controlled trial. J Gerontol A Biol Sci Med Sci. 2006;61(2):176-81.

Study Characteristics	Population	Intervention Groups	Results		Comments
			Measure	Outcome	
Pitkala KH 2006 **Finland** **Setting** General medicine units (6) City Hospital **Study Design** RCT **Randomization method** Computer generated random numbers assigned consecutively by blinded staff member **Study Length/Start-Stop Dates** 9/2001-11/2002 **Purpose** To investigate whether a comprehensive geriatric assessment and individually tailored treatment are effective in reducing mortality and permanent institutional care among patients with delirium. Also to determine whether this treatment is beneficial in reducing the number of days spent in institutions, alleviating delirium, or improving cognition or physical functioning of these patients. **Funding source(s):** Lions Organization, Helsinki University Central Hospital, Academy of Finland **Quality Score**: 7 **Risk of Bias**: Unclear	**N = 2040 admitted (>69 yr)** n = 350 not eligible for screening N = 1690 screened N = 379 CAM positive n = 205 excluded **N = 174 met DSM IV criteria** n = 87 intervention n = 87 control **Inclusion** Age >69 Informed consent from closest proxy **Exclusion** N = (see below) *Not screened (305)* n = 118 admission from permanent institutional care facility n = 202 discharged <48 h n = 30 refused screening *Screened/excluded* n = 23 refused n = 24 terminal prognosis n = 4 discharged before delirium dx confirmed n = 10 permanent institutional care n = 15 no caregiver/consent n = 129 did not meet DSM IV criteria **All patients protocol** Screened within 2 days of admission (baseline) -CAM, MMSE, Digit Span -proxy interview -premorbid dementia status (CDRS; DSM IV) -med record review -comorbidities (CMI) Follow up at 3&7 6 months -MMSE -Barthel Index -IADL scale -Geriatric Depression Scale -Mini-Nutritional Assessment -proxy interview	**n = 87 intervention** n = 87 follow up 3 & 6 months Men and women (75.9%) Mean age 83.8 (5.6) 1. Accurate dx of delirium 2. Comprehensive geriatric assessment 3. Avoid conventional neuroleptics in favor of atypical antipsychotics 4. Orientation 5. Physiotherapy 6. General geriatric interventions -nutritional supplements -calcium + vitamin D -hip protectors 7. Cholinesterase inhibitors if MMSE <23 -also MRI or CT if cognition impaired after delirium resolution 8. Comprehensive discharge planning -consultation with social worker -occupational therapist home visit -discharge planning with caregiver(s)	**Delirium assessment:** CAM MMSE Digit Span DSM IV Memorial Delirium Assessment Scale (MDAS) **Baseline characteristics** **Primary outcomes** Atypical antipsychotics Conventional neuroleptics Acetylcholinesterase inhibitors Vitamin D + calcium Nutritional supplements Hip protectors Physical therapy Specialist consultations CT or MRI scans Intensity and severity of delirium symptoms improved at 6 months (MMSE score) Delirium days (mean, SD) Deceased Admitted to permanent institutional care	Admission screen by 2 trained study nurses following standardized procedures using CAM and MMSE; positive CAM assessed by study physician; delirium dx confirmed by DSM IV criteria. Daily MDAS during first week in hospital and every second day thereafter No significant differences between groups **Significant difference in treatment interventions % vs %, p** **Intervention (87) vs Control (87)** 69.0% vs 29.9%. p <.001 8.0% vs 23,.0%, p = .006 58.5% vs 9.3%, p <.001 77.0% vs 9.3%, p <.001 92.0% vs 0.0%, p <.001 90.8% vs 1.1%, p <.001 89.7% vs 44.8%, p <.001 49.4% vs 28.7%, p = .005 51.7% vs 8.0%, p <.001 18.4 vs 15.8, p = 0.047 **No significant difference between groups** 29.3 (25.6) vs 22.4 (18,.4), p = .171 34.5% vs 29.9%, p = .516 42.5% vs 51.7%, p = .224	Systematic methods on screening or preventing delirium are not used in the study hospital This intervention did not improve patients' general prognosis as indicated by no effect on mortality, institutionalization or length of hospital stay with delirium In the case of full blown delirium, this type of intervention may be "too little too late" to produce a significant difference in prognosis and thus, even more effort should be focused on prevention of delirium among such patients. Post hoc analysis of patient and intervention factors impacting prognosis: -Barthel Index score significant for mortality HR 2.1 (1.1-4.0) -nutritional supplements protected against death HR 0.3 (0.1-0.8) Antipsychotics and ChEIs did not affect mortality
		n = 87 control n = 83 follow up 3 & 6 months n = 4 refused assessments but allowed medical record retrieval of endpoint data Men and women (71.3%) Mean age 83.3 (6.2) Usual care	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Secondary outcomes**		
Conclusion: This study is the third randomized trial showing no effect of geriatric intervention on the prognosis for delirium. Good, comprehensive geriatric treatment is justified in this patient group because of more effective alleviation of delirium and improved cognition. However, individual cases deserve careful tailoring of treatment and evaluation whether they benefit from active, curative treatment or good palliative care.					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	No comment on blinded outcome assessment
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	1	Low	
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = Unclear**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 7**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G3-G5-Mudge AM, Maussen C, Duncan J, Denaro CP**.** Improving quality of delirium care in a general medical service with established interdisciplinary care: a controlled trial. Intern Med J. 2013;43(3):270-7.

Study Characteristics	Population	Intervention Groups	Results		Comments
			Measure	**Outcome**	
Mudge AM 2013 Australia **Setting** Metropolitan teaching hospital **Study Design** Concurrent controlled trial **Selection method** Patients admitted to intervention or control unit screened positive for delirium or had ≥2 delirium on initial screening **Study Length/Start-Stop Dates** Not described **Purpose** To implement delirium guidelines in general medical patients to reduce incidence and duration of delirium and improve outcomes in delirious patients. **Funding source(s):** Queensland Health Strengthening Aged Care initiative **Quality Score** 4 **Risk of Bias**: High	**N = 415 admissions** n = 209 excluded (see below) N = 206 risk screening **N = 136 at risk for delirium** n = 62 admitted to intervention unit n = 74 admitted to control units **Inclusion** Age ≥65 Admitted to intervention or control units Anticipated LOS ≥3 days Informed consent (patient or proxy) **Exclusion** N = 209 n = 21 Critically ill n = 27 Previously documented severe dementia (MMSE <10) n = 20 -Psychiatric disability -Intellectual disability -Dysphasia n = 34 Not English speaking n = 15 other n = 92 Refused or unable to obtain proxy consent Required palliative care Unconscious **Blinding** Project staff were aware of group assignment **Analysis** Confined to participants who were delirious or had ≥2 risk factors for delirium on initial screening **Intervention Multi-disciplinary Steering Committee** Leader – consultant physician from intervention ward Prioritized activities Planned specific strategies Identify/address barriers Assess progress	**n = 62 intervention unit** **n = 19 delirium dx** **n = 43 at risk for delirium** Men and women (51.6%) Mean age 79.6 (8.2) *Unit chosen because of* -a consistent occupancy by a single medical team -presence of identifiable medical and nursing champions *Intervention strategies (see detail Table 1)* -Delirium risk factor screening -Delirium detection -Education and training -Ward-based strategies -Team strategies -Patient/carer information *Intervention implementation phases* -establishment and planning -project staff recruitment --development of screening tools -development of education programs -implementation phase -evaluation phase	**Delirium assessment:** CAM **Baseline characteristics** Impaired cognition Impaired vision or hearing Dehydration Hyponatremia CAM screening within 48 h Prevalent delirium Age ADL dependence before acute illness **Primary outcomes** > 3 ward moves reduced Incident delirium during admission Trend to longer LOS (median) Psychogeriatric consultation Use of restraints **Outcomes for delirium subjects** LOS acute stay(days) LOS hospital stay (days) Inpatient mortality Falls Persistent delirium at discharge	CAM administered to all delirious and at risk patients by trained project staff within 48 h of admission and twice weekly throughout hospital stay **No significant difference between groups** **Intervention (62) vs control (74)** 51.6% vs 56.8% 100% vs 98.6% 59.7% vs 50.0% 21.0% vs 16.2% 77.4% vs 83.8% 30.6% vs36.45 **Significant difference between groups** **Delirious vs at risk** 83.1 vs 80.0, p = 0.02 67% vs 43%, p = 0.008 **Intervention (62) vs control (74)** 34% vs 51%, p = 0.05 0% vs 0% 11 days vs 8 days, p = 0.07 32% vs 11%, p = 0.04 0% vs 0% **Intervention (19) vs control (27)** 16 (12-20) vs 8 (4-20), p = 0.01 NS 16 (13-26) vs 10 (4-24), p = 0.11 Trend 0% vs 18.5%, p = 0.07 NS 10.5% vs 22.2%, p = 0.16 31.6% vs 70.8%, p = 0.02	No significant difference for all intervention (62) vs control (74): -Acute LOS -Hospital LOS -Inpatient mortality -Falls The trends toward improved in hospital mortality and falls were encouraging but must be interpreted with caution given the small sample size. The low incidence of new delirium, low mortality in the delirious cohort and limited evidence of process improvements may reflect the effectiveness of the existing interdisciplinary model of care rather than ineffective guideline recommendations or poor implementation. Although no new delirium cases were identified reassessment was done only twice a week, so incident cases may have been missed Delirium duration could not be adequately assessed because of the number of participants discharged with persisting delirium. Although there was a delirium bay (4 beds) in the intervention group, there was not specific analysis of patients who were assigned to these beds.
		n = 74 control units **n = 27 delirium dx** **n = 47 at risk for delirium** Men and women (48.6%) Mean age 82.3 (7.7) Unit chosen because of -close proximity to intervention unit -similar staffing and policies Usual care	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Secondary outcomes**	See above See above See above See above	
Conclusion: By implementing clinical practice guidelines for delirium on a single medical ward, there was a marked reduction in discharge of persistently delirious patients in the intervention group, but this resulted in a longer hospital stay and there was no reduction seen in one-on-one nursing use, so the intervention was costly					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	Unclear	Although there were no significant differences between intervention groups there were differences between delirious and at risk patients
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	Allocation not concealed
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	Study staff not blinded
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Baseline imbalances Possible confounders (such as infrequent CAM administration) Controlled trial; not RCT
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 4**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
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  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G5-Young LJ, George J. Do guidelines improve the process and outcomes of care in delirium? Age Ageing. 2003;32(5):525-8.

Study Characteristics	Population	Study Process	Results		Comments
			Measure	Outcome	
Young LJ 2003 **UK** **Setting** Multicenter (5) Urban District General Hospitals **Study Design** Baseline observational study ("before"); consensus guideline development; randomized implementation "after" study **Selection method** All patients meeting inclusion criteria Clinical data from medical and nursing notes Research registrar allocated hospital to low; medium, high intervention **Study Length/Start-Stop Dates** 3 months baseline 3 months implementation Concurrent time periods **Purpose** To devise guidelines for optimal management of delirium in clinical practice and to evaluate whether guidelines improve the process and outcomes of care. **Funding source(s):** National Audit monies **Quality Score:** 3 **Risk of Bias:** High	**Baseline study** **N = 211** Men and women (64%) Mean age 81.5 (7.3) Dementia = 47% **Implementation of guidelines** N = 147 Med/low n = 110 Med/low before n = 37 Med/ low after N = 189 High n = 101 before n = 88 after **Inclusion** Age ≥65 Admitted to general medical ward Admitted to elderly care ward Screened for delirium on admission (CAM) **Exclusion** Not discussed **Assessments** Usual Cognitive Status (UCS) Mental Test Score (MTS)	**Collection of data from baseline study** **Data recorded** -delirium dx -length of stay -use of mental test score -use of sedation -use of orientation cues (clocks and calendars) -assessment of vision -assessment of hearing -alcohol history -complications -ward moves **Development of guidelines** -multidisciplinary consensus -Literature search (MEDLINE, BIDS) -revision of consensus to include evidence from literature search -formal multidisciplinary consensus process (Delphi technique) -including caregivers of patients who had experienced delirium -high degree of agreement on all recommendations -final guidelines approved by British Geriatrics Society **Implementation of guidelines** -baseline study repeated in the 5 hospitals -3 levels of intervention -low = feedback of baseline data -medium feedback of baseline data and distribution of guidelines to nurses and doctors -high = as medium but also teaching sessions for nurses and doctors in each center **Hospitals randomized**: N = 1 low intervention N = 2 medium intervention N = 2 high intervention Process and outcomes of care recorded as in the baseline study	**Delirium assessment:** CAM DSM IV **Baseline study characteristics** Delirium dx recorded Cot sides associations (higher mortality) (more falls) (more pressure sores) (more infections) (longer LOS) **Implementation of guidelines** All measures Age Hearing recorded Mean LOS (d) MTS completed	Screened for delirium using the CAM (and DSM IV criteria); no discussion of ongoing assessment **Significant differences** More often when UCS was recorded 72% vs 42.9%, p <0.001 More often when MTS attempted 73.4% vs 51.4%, p = 0.005 **Significant correlations** 37.3% vs 21.2%, p = 0.02 43.8% vs 22.1%, p = 0.002 29.7% vs 14.4%, p = 0.014 50% vs 24.4%, p = 0.0004 21 (11-36) vs 15 (7-28), p = 0.008 **Hospital allocation (before vs after)** **Med/low before vs Med/low after** **N = 110 vs 37** No significant differences before vs after **Significant differences** **High before vs High after** **N = 101 vs 88** 80.6 (7,3) vs 82,.9 (7.1) p = 0.02 5% vs 15.9%, p = 0.02 **Trend toward significant difference** **High before vs High after** **N = 101 vs 88** 16 (8-30 vs 10.5 (5-29), p 0.07 16.8% vs 27.9%, p 0.07 Delirium was recorded in only 26% of nursing notes and 50% of medical notes There was evidence of poor management with frequent moves between wards and using restraints (cot sides). There was a poor process of care as use of cot sides seemed to be related to poor outcomes	Delirium is a poorly managed condition in hospital with a high use of sedation, cot-sides, frequent ward moves and failure to use orientation techniques Poor management of delirium is reflected in a high mortality, frequent complications and long lengths of stay Guidelines alone do not appear to improve management of delirium; educational and organizational change is also required

Conclusion: Delirium is a poorly managed condition in older people and guidelines alone fail to improve the process and outcomes of care.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	Significant differences between groups in baseline study and in implementation study
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	Baseline study = retrospective data Implementation study unclear
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	Unclear	Baseline study = retrospective
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Before/after study Baseline and implementation imbalances ? presence of confounders ? RCT for implementation/ no ITT
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING =**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	0		Only 37 patients in med/low after
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE =**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G2-Vaurio LE, Sands LP, Wang Y, et al. Postoperative delirium: the importance of pain and pain management. Anesth Analg. 2006;102(4):1267-73.

Study Characteristics	Population	Study Groups	Results		Comments
			Measure	Outcome	
VaurioLE 2006 **USA** **Setting** University Hospital **Study Design** Comparative Study **Selection method** Consecutive patients scheduled for major elective noncardiac surgery requiring anesthesia **Study Length/Start-Stop Dates** 2001-2004 **Purpose** To determine whether both postoperative pain and pain management method had an independent association with the development of postoperative delirium. **Funding source(s):** NIH Grant **Quality Score** 3 **Risk of Bias**: High	**N = 333** n = 31 not reported in delirium vs no delirium comparison **N = 302 analyzed** n = 36 n = 74 **Inclusion** Age ≥65 Elective noncardiac surgery Anesthesia required Expected LOS >48h Informed consent **Exclusion** N = not described Not capable of providing or refusing to provide informed consent **Pain measurement** Structured interviews by research assistants -verbal VAS -0 = no pain -1-4 = moderate pain -5-10 = severe pain Pain recorded -Pre-op -POD1 (24 h after surgery) -POD2 (48 h after surgery) -pain at rest -pain with movement Significant change = ≥2 point increase from baseline **Pain management** Attending physician control -PCA -neuraxial (epidural or intrathecal) -oral opioids -combination Type and daily dose of opioids recorded POD1-3 Type and dose of other analgesics recorded **Assessment covariates** Pre-op -TICS -GDS -ADLs and IADLs -comorbidities (med record and Charlson Comorbidity Index) -type of surgery ASA class etc	**n = 144 delirium** Men and women (64%) Age ≥ 70 (n) = 36 Age >70 (n) = 108 Independent in 7 IADLs Yes (n) = 71 TICS score (mean) 30.9 GDS score 0-2 = 77 3-5 = 44 ≥6 = 23 Education High school or less = 50 HS grad or greater = 91 ASA classification 1-2 = 60 3-4 = 84 Surgery type Neur/ortho = 86; Urol = 14 Gyn = 17; Vasc = 7 Gen/ENT/Plas = 19	**Delirium assessment:** CAM **Baseline characteristics** Mean age (SD) Preoperative chronic pain Moderate at rest Severe at rest Moderate to severe on movement Preoperative oral narcotics **Outcomes** Developed delirium post op Age Gender Independent in 7 IADLs TICS score GDS score Education ASA classification Type of surgery	Trained interviewers determined the presence of delirium pre-op, POD1 and POD2. All delirium assessments were validated by a second investigator. All patients 74 (6), range 65-96 27.3% 17% 63.3% 23% 46% of all patients **Significant difference between groups (Bivariate analysis)** **Delirium vs no delirium (p)** <0.0001 0.0001 0.002 0.008 0.03 0.003 0.015 0.024	Postoperative pain and pain management strategies are independently associated with the development of postoperative delirium. Both the presence of postoperative pain and increased pain postoperatively are independent predictors of postoperative delirium There was an ordered relationship between levels of preoperative pain and the risk for development of postoperative delirium. Severe preoperative pain was associated with greater odds of developing delirium than was moderate pain. This finding highlights the importance of considering and perhaps treating both preoperative chronic pain levels and postoperative pain levels IV PCA and neuraxial analgesics conferred equal risk in the development of delirium. In contrast, patients who received oral opioid analgesics were at decreased risk for delirium vs those receiving PDA. All of the commonly used opioid analgesics have a similar effect on the development of postoperative delirium.
		n = 158 no delirium Men and women (42%) Age ≥ 70 (n) = 74 Age >70 (n) = 84 Independent in 7 IADLs Yes = 109 TICS score (mean) 32.3 GDS score 0-2 = 104 3-5 = 38 ≥6 = 16 Education High school or less = 31 HS grad or greater = 123 ASA classification 1-2 = 88 3-4 = 70 Surgery type Neur/ortho = 76; Urol = 37 Gyn = 17; Vasc = 11 Gen/ENT/Plas = 17	**Delirium assessment:** **Outcomes (continued)** **Factors associated with post-operative delirium** Preoperative pain at rest Moderate Severe Increase in pain POD1 Mode of postop analgesia PCA or combination (n) Neuraxial (n) Oral narcotics Oral narcotic use POD1 No (n) Yes (n) Any benzodiazepine post op No (n) Yes (n) Any other CNS drug post op No (n) Yes (n)	See above **Significant difference between groups** **Delirium vs no delirium** 0.007 OR 2.2 (1.2-4.0) OR 3.7 (1.5-9.0) OR 1.1 (1.01-1.2), p 0.002 0,002 109 vs 93 18 vs 24 16 vs 41 0.058 86 vs 77 51 vs 72 0.01 93 vs 120 44 vs 28 0.0003 67 vs 104 69 vs 44	
Conclusion: Postoperative events are more important than the type of anesthesia. Levels of preoperative pain and postoperative increase in pain levels are independent predictors of the development of postoperative delirium in elderly surgical patients. Elderly surgical patients with substantial preoperative baseline pain should be targeted for more intensive pain control or addition of adjuvant analgesia postoperatively.					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	Baseline characteristics not compared except as they relate to the development of delirium; these had significant differences; other differences may confound these findings
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	Unclear	NA Observational study
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	Unclear	NA – observational study
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	High	Original N = 333 Analysis N = 302 (no explanation of difference)
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Unknown baseline differences other than as related to delirium/no delirium Unknown other confounders may be present
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 3**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G2-Lynch EP, Lazor MA, Gellis JE, et al. The impact of postoperative pain on the development of postoperative delirium. Anesth Analg. 1998;86(4):781-5.

Study Characteristics	Population	Surgery/delirium incidence		Results		Adverse Effects
				Measure	**Outcome**	
Lynch 1998 **USA** **Setting** University Hospital **Study Design** Prospective observational study **Selection method** Consecutive (all) patients meeting inclusion criteria **Study Length/Start-Stop Dates** 12/1992 to 6/1993 **Purpose** To examine the role of postoperative pain and its treatment on the development of postoperative delirium. **Funding source(s):** Agency for Health Care Policy and Research Grant ROI-H506573 **Quality Score** 2 **Risk of Bias**: High	**N = 361** Men 52% Mean age 66 (8) TICS score: 33.6 (3.2) TICS <30: 11% SAS class I: 124 (35%) SAS class II : 101 (29%) SAS class III : 107 (31%) SAS class IV : 18 (5%) Abnormal serum chemistries: 11 (3%) History of alcohol abuse: 13 (4%) **Inclusion** >50 yrs Underwent major elective noncardiac operations Expected stay >2 ds English speaking **Exclusion** N = not described With delirium pre-op **Pre op assessment:** Cognitive status -TICS (Telephone Interview of Cognitive Status) Physical function: -SAS (Specific Activity Scale **Post op assessment:** -Review medical record data from MEDICUS Hospital's nursing intensity index -Pain (VAS, 0-10) -pain at rest, -pain with movement, -maximal pain over the previous 24 h	**Procedure**	**no. of patients (% with delirium)**	**Delirium assessment:** CAM n = 17 dx by CAM n = 5 dx by chart/MEDICUS n = 12 dx by both **Baseline characteristics** **Primary outcomes** **Delirium** Day 1 Day 2 Day 3 Days l-3 **Secondary outcomes** Rest pain day 1 Rest pain day 2 Rest pain day 3 Movement pain day 1 Movement pain day 2 Movement pain day 3 Maximal pain day 1 Maximal pain day 2 Maximal pain day 3 dose of opioid in morphine equivalents **Controlled for procedure** Rest pain Movement pain Maximal pain **Controlled for risk factors * and procedure** Rest pain Movement pain Maximal pain The method of postoperative analgesia (epidural, patient-controlled analgesia, parenteral, oral, or none),	Performed CAM daily on Post op Days 1, 2, and 3 based on the interview or if data from the medical record and the hospital's nursing intensity index documented delirium. Inter-rater reliability and delirium severity were not discussed. See intervention column (delirium vs no delirium groups' baseline characteristics not compared) **Incidence / Prevalence** 12 (3.3%) / 12 (3.3%) 16 (4.6%) / 23 (6.4%) 6 (1.8%) / 17 (4.7%) 34 (9.4%) **Delirious vs Not Delirious** 3.8 (3.8) vs 2.7 (2.4), P = 0.38 4.4(3.4) vs 2.3 (2.4), P = 0.008 3.6 (3.2) vs 2.4 (2.5), P = 0.37 3.6 (3.8) vs 4.6 (3.0), P = 0.32 6.8 (2.3) vs 4.3 (2.9), P= 0.006 5.0 (3.6) vs 4.2 (2.8), P = 0.53 6.8 (3.9) vs 6.4 (3.0), P = 0.65 7.9 (1.8) vs 5.8 (2.9), P = 0.03 6.5 (3.0) vs 5.6 (3.0), P = 0.59 30.0 (26.2) vs 25.5 (22.6), p= 0.50 **Risk ratio** 1.20 (1.04,1.37); p= 0.015 1.09 (0.95,1.26); p= 0.23 1.14 (0.97,1.33) ; p=0.10 1.20 (1.01,1.43); p= 0.04 1.07 (0.91,1.25); p= 0.42 1.11 (0.94,1.29) ; p=0.23 not associated with an increased risk of delirium.	**Comments:** The author performed daily interviews in a large population of patients undergoing noncardiac surgery to measure their level of pain and development of delirium. The author found an association between higher pain levels at rest and the development of delirium. The results suggest that better control of postoperative pain may reduce this serious complication. Increased pain at rest was the only type of pain associated with an increased risk of developing delirium. Although pain with movement or maximal pain may represent more of an acute physiologic stress, patients experience pain at rest for more hours of the day. Therefore, pain at rest is more likely to affect their sleep-wake cycle and hormonal milieu. In this study, there was a higher percentage of missing pain scores among delirious patients (29% vs 1.4%); therefore, it seems that delirium accounts for most of the missing scores.
		Colectomy Exploratory laparotomy Mastectomy Total hip replacement Total knee replacement Abdominal aortic aneurysm Carotid endarterectomy Peripheral vascular Radical prostatectomy Laminectomy Hysterectomy Thoracotomy Aorto-bifemoral bypass Thoracoscopic lung resection Total	21 (14.3%) 26 (11.5%) 12 (0.9%) 66 (6%) 58 (15.5%) 17 (5.9%) 19 (5.3%) 18 (22.2%) 30 (0%) 11 18.2%) 11 (9.1%) 43 (7%) 7 (0%) 22 (13.6%) 361 (9.4%)				
				* The risk factors for which we controlled are: age, preoperative cognitive status, Specific Activity Scale class, abnormal electrolytes, and alcohol abuse.		
Conclusion: Increased postoperative pain at rest was associated with postoperative delirium. Unlike unmodifiable risk factors for delirium, the quality of postoperative analgesia can be improved and therefore the incidence of postoperative delirium decreased.						

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	No baseline comparison between groups of delirious vs nondelirious patients
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	NA - Observational studies
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	NA - Observational studies
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	High	Exclusions not described
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o Lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	Unclear	Unclear how baseline confounders may have affected results
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	0		CAM not used for all patients
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 2**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G2-Leung JM, Sands LP, Rico M, et al. Pilot clinical trial of gabapentin to decrease postoperative delirium in older patients. Neurology. 2006b;67(7):1251-3.

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects
			Measure	Outcome	
Leung 2006b **Denmark** **Setting** Academic hospital. **Study Design** Pilot RCT - double-blind, placebo-controlled **Randomization method** A computerized random number list was created **Study Length/Start-Stop Dates** 2005 - first 3 postoperative days **Purpose** To assess safety and feasibility to enable a subsequent larger trial to be conducted to compare the incidence of postoperative delirium in patients given gabapentin vs . placebo and to determine if the rates of delirium vary with differences in pain severity and opioid consumption **Funding source(s):** Institutional funds and the NIA, NIH Grant #1K24 AG00948-05 **Quality Score** 5 **Risk of Bias**: High	**N = 21** n = 9 gabapentin n = 12 placebo **Inclusion** Age >45 yrs Undergoing surgery involving the spine Requiring general anesthesia Stay in the hospital > 72hrs. **Exclusion** N = not described Could not complete the delirium testing Taking preoperative gabapentin Sensitivity to gabapentin. **Pain assessment:** Verbal VAS (0-10) during the last 24 h - at rest -average, -minimum pain -maximum pain **Assessment pre-op** ADL Scale: (Katz) IADL Scale : (Lawton-Brody) TICS: (Telephone Interview for Cognitive Status) GDS: (Geriatric Depression Scale) ASA classification	**n = 9 Gabapentin group** Men/women 4/5 Mean age 57.2 (10.3) Either gabapentin 900 mg or placebo was administered by mouth 1 to 2 hours before surgery and anesthesia. This dose was continued for the first 3 postoperative days. Intraoperative anesthetic for all patients was standardized to IV anesthetics and a low dose inhalational agent. Postoperatively, all patients received on-demand patient controlled analgesia (PCA) with IV hydromorphone.	**Delirium assessment:** CAM RASS **Baseline characteristics** demographic information Independent in 5 ADLs Independent in 7 IADLs TICS score GDS score Charlson Comorbidity Index No. preopcomorbid conditions Preoperative opioid use **Primary outcomes** incidence of post-op delirium Preoperative vs post operative VAS **Secondary outcomes** Post-op PCA hydromorphone pain levels Day of surgery (n = 21) POD1 (n = 21) POD 2 (n = 20) POD 3 (n = 17) Time x drug	Trained interviewer performed CAM daily based on cog test and validated by a second investigator. Inter-rater reliability **Gabapentin vs placebo** no significant difference 8 vs 12; p=1.0 6 vs 7 ; p=0.43 33.6 (2.6) vs 34.5 (3.0);p= 0.47 3.9 (2.3) vs 6.2 (4.9); p= 0.18 1.2(1.9) vs 0.5 (1.0); p= 0.28 2.3 (1.5) vs 1.8 (1.2); p= 0.40 5 vs 8; p= 0.60 0/9 (0%) vs 5/12 (42%) p= 0.045 no significant difference between groups on any POD trend toward a reduced use similar in 2 groups **Gabapentin vs placebo** 2.68 (2.24 vs 3.32 (3,95) 2,78 (2.26) vs 13.54 (25.31) 2.47 (3.65) vs 7.86 (15.20) 1.84 (2.73) vs 1.02 (2.35) p = 0.37 (2.26)	None of the patients had agitated delirium as defined by the Richmond agitation-sedation score. Two patients (one in each group) had postoperative sedation reported. No patient had dizziness, nystagmus, or ataxia. **Comments:** In surgical pain models and in clinical studies of inflammatory pain that produce allodynia and hyperalgesia, gabapentin and its analogs improve pain. These findings suggest that sensitization of dorsal horn neurons may be an important mechanism for pain in the early postoperative period. In addition, antihyperalgesic drugs could improve post-operative analgesics, as they may block pathologic pain while leaving other protective nociceptive mechanisms intact
		n = 12 Placebo group Men/ women 7/5 Mean age 61.4 (11.3) See above	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Secondary outcomes**	See above See above See above See above	
Conclusion: In this small study, gabapentin was safe and was associated with a significantly lower incidence of postoperative delirium.					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	1	Low	
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	High	Number of exclusions not described
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	No ITT analysis (low N)
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	0		<50 total patients
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 5**

Instructions on rating:

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- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
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  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G1-G2-G3- Krenk L, Rasmussen LS, Hansen TB, et al. Delirium after fast-track hip and knee arthroplasty. Br J Anaesth. 2012a;108(4):607-11.

Study Characteristics	Population	Standard Protocols	Results		Comments
			Measure	Outcome	
Kren kL 2012 **Denmark** **Setting** Multicenter 4 hospitals **Study Design** prospective multicentre study **Selection method** Not described **Study Length/Start-Stop Dates** 2/2010 to8/ 2011 **Purpose** To evaluate the incidence of postoperative delirium (PD) after fast-track hip (THA) and knee arthroplasty (TKA) with anticipated length of stay (LOS) of <3 days. **Funding source(s):** Supported by the Lundbeck Foundation. **Quality Score** 2 **Risk of Bias**: High	**N = 225 enrolled** n = 84 declined to participate n = 2 MMSE<24 Baseline characteristics reported = 225 Follow up = 220 n = 81 TKA n = 144 THA Men and women (51%) Mean age 69.4 (60–86) **Inclusion** undergoing elective THA and TKA anticipated length of stay (LOS) <3 days Age >60 yr ASA class I–IV. Fluent in written and spoken Danish. **Exclusion** N = 86 Anaesthetized in 30 days n = 2 dementia [MMSE ⩽ 23] Parkinson's disease neurological disease functional impairment. alcohol abuse daily use of hypnotics or anxiolytics severe hearing or visual impairment. n = 84 declined to enroll	All patients received standardized anaesthesia and postoperative analgesia according to the centre they were affiliated to. All patients fasted for 6 h without solids and 2 h without clear liquids. No patients were given sedative premedication. All patients received standardized postoperative care with well-defined discharge criteria Postoperative analgesia according to hospital protocol (= n patients) -opioids in PACU = 117 -oxycodone in hospital = 135 -morphine in hospital = 77 -other opioid (ketobemidone) = 5	**Delirium assessment:** DSM-IV **Baseline characteristics** MMSE ASA I/II/III/IV BMI (kg m-2) Smoking daily Alcohol .2 units per day Hypertension Lung disease Heart disease Diabetes (type I/II) Depression Length of stay (days) **Primary outcomes** incidence of delirium **Secondary outcomes** postoperative complications	Nursing staff were trained to focus on symptoms of delirium and evaluate delirium every 8 h shift based on DSM-IV criteria. Inter-rater reliability and delirium severity were not discussed. N = 225 28.6 (24–30) 69/143/13/0 27.3 (17–40) 22 (9.7%) 24 (10.6%) 126 (56.0%) 15 (6.7%) 28 (12.4%) 1/17 17 (7.5%) 2.6 (1–8) No patients developed delirium during their hospital stay 0.0 (0.0–1.6%) or at their follow up visit (n=220) Within the first postop week -1 = re-operation due to wound complications -2 = re-operation with debridement -3 = superficial wound infection -2 = gastric ulcer -6 blood transfusions All patients discharged to home No readmissions or other complications (median 12.0 days; range 5-36 dayus)	**Comments:** This study reports no cases of PD in an elderly patient population after fast-track elective THA and TKA during hospitalization and 1–2 weeks follow-up. The fast-track set-up has reduced LOS from 7 to 10 days to a median of 3 days in a decade after hip or knee arthroplasty. This study studied only the subset of arthroplasty patients with MMSE >23 in a fast-track set-up. Inclusion was not consecutive because the research staff was only capable of evaluating four patients per week, and when this number was reached, no more patients were asked to participate that week. A single patient had a LOS of 8 days: this was due to reoperation 4 days after primary surgery. Overall median LOS was 2 days.
Conclusion: A fast-track set-up with multimodal opioid-sparing analgesia was associated with lack of postoperative delirium after elective hip and knee arthroplasty in elderly patients.					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	Observational study
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	Observational study
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	Observational study
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	High	Not described exclusion
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o Lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Observational study No comparison group Unknown if confounders exist
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	0		Single group (no comparison)
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 2**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
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  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G2-Agostini JV, Leo-Summers LS, Inouye SK. Cognitive and other adverse effects of diphenhydramine use in hospitalized older patients. Arch Intern Med. 2001;161(17):2091-7.

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects
			Measure	**Outcome**	
Agostini 2001 **USA** **Setting** university hospital **Study Design** prospective cohort study **Selection method** Consecutive admissions of older patients, divided into 2 groups by diphenhydramine exposure. **Study Length/Start-Stop Dates** 3/1995 to 2/1998 **Purpose** To examine the rate of diphenhydramine use in a large prospective cohort of elderly hospitalized patients; to evaluate potential adverse outcomes (eg, cognitive, behavioral, and other anticholinergic effects) associated with diphenhydramine use; and to describe current diphenhydramine use in the study cohort. **Funding source(s):** NIA RO1AG12551 P60AG10469 K24AG00949 DF98-105 **Quality Score** 6 **Risk of Bias**: Unclear	**N = 426** n = 114 diphenhydramine exposed n = 312 diphenhydramine nonexposed **Inclusion** >70 yrs with no baseline delirium **Exclusion** N = not described profound dementia discharge or death in 48 hrs non-English speakers. **Assessment:** MMSE Chart review Charlson comorbidity scores APACHE II ADL	**n = 114 Diphenhydramine-Exposed Group** Men 48 (42%) Mean age 80.3 ± 5.6 Race, white: 101 (89%) Admitted from: Home 107 (94%) Nursing home 6 (5%) Received a mean of 2.1 doses, with 97% of dose administered orally while hospitalized. The maximum cumulative daily dose for any given patient was 100 mg.	**Delirium assessment:** Confusion Assessment Method (CAM) **Baseline characteristics** Mean ± SD APACHE II score *Baseline delirium risk* Intermediate High MMSE No. of medications impairment in ADLs No. of diagnoses Baseline sleeping difficulty **Primary outcomes** Delirium symptoms* CAM delirium criteria *Increased risk delirium symptoms* Inattention* Disorganized speech* Altered level of consciousness* Abnormal psychomotor activity* Altered sleep wake cycle* Behavioral disturbance* **Secondary outcomes (other risks)** New urinary catheter* Length of stay >7 d* Diphenhydramine doses * multiple logistic regression model controlled for age, sex, and baseline, delirium risk (all significant p <.05)	Trained RAs daily rating CAM and the MMSE score. Inter-rater reliability and delirium severity were not discussed. **Exposed (114) vs Nonexposed(312)** No significant differences 15.6 ± 4.2 vs 15.6 ± 4.1 87 (76%) vs 220 (71%) 27 (24%) vs 92 (29%) 23.6 ± 4.7 vs 23.0 ± 5.0 5.4 ± 3.1 vs 5.6 ± 3.2 28 (25%) vs 70 (22%) 8.0 ± 2.8 vs 7.5 ± 2.8 55 (50%) vs 141 (46%) **[RR, 95% CI]; n(%)** 1.7 (1.3-2.3]; 47 (42%) vs 75 (24%) P <.051 2.1 (0.9-4.7]; 9 (8%) vs 12 (4%) OR: 2.3 (1.4-3.6) **Use of diphenhydramine RR (CI)** 3,.0 (1.5-5.9) 5.5 (1.0-29.8) 3.1 (1.6-6.1) 2.3 (1.1-4.5) 2.0 (1.2-3.3) 5.6 (1.0-29.2) RR (CI) 2.8 (0.4-4,.19) 1.3 (1.0-1.6) 237 (mean 2.1 doses/patient) -24% were given inappropriately) -50 doses for transfusion prophylaxis -6doses to patients with obstructive urinary symptoms Dose response + significant trend toward cognitive decline and increasing dosage	**See outcomes** **Comments:** The delirium symptoms reported in this study likely capture more subtle and partial forms of delirium that do not meet full delirium criteria. The CAM criteria were limited to a 1-time observation, whereas the recognition of these delirium symptoms allowed the detection of more subtle changes in cognitive functioning over any 48-hour period following diphenhydramine exposure. The results suggest that the clinician's review of a patient's list of daily medications to remove the "routine" or "as needed for sleep" prescriptions is critically important in reducing unwanted outcomes such as cognitive decline. This study derived strength from the prospective cohort design that provided precise data on exposures, eliminated recall bias, and provided carefully documented outcomes from daily interviews. One limitation of this study was the difficulty in controlling for other concurrently administered pharmacotherapies during hospitalization.
		n = 312 Diphenhydramine-Nonexposed Group Men 119 (38%) Mean age 79.6 ± 6.4 Race, white: 261 (84) Describe intervention Admitted from: Home 288 (92%) Nursing home 21 (7%) Did not receive diphenhydramine during hospitalization	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Secondary outcomes**	See above See above See above See above	

Conclusion: Diphenhydramine administration in older hospitalized patients is associated with an increased risk of cognitive decline and other adverse effects with a dose response relationship. Careful review of its use is necessary in this vulnerable population.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	Unclear	NA-prospective cohort, but no significant differences in baseline characteristics between groups
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	Unclear	NA-observational study
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	1	Low	
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	1	Low	
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = Unclear**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 6**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G2-Marcantonio ER, Juarez G, Goldman L, et al. The relationship of postoperative delirium with psychoactive medications. JAMA 1994;272(19):1518-1522.

Study Characteristics	Population	Study Groups	Results		Comments
			Measure	**Outcome**	
Marcantonio ER 1994 USA **Setting** University Hospital (General, Orthopedic and Gynecologic Surgery Depts) **Study Design** Prospective cohort (nested case control **Selection method** Cases and controls derived from a prospective cohort study of patients consenting to preoperative evaluation **Study Length/Start-Stop Dates** 11/1990-3/2002 **Purpose** To determine whether post-operative exposures to certain medications were independently associated with delirium, after controlling for pre-operative risk **Funding source(s):** Grant funding -Agency for Health Care Policy and Research -National Research Service Award for Research in Primary Care Medicine -Established Investigator Award (AHA) **Quality Score** 5 **Risk of Bias**: Unclear	**N = 1341 in prospective cohort** **N = 245 delirium +no delirium** n = 91 delirium n = 154 no delirium **Inclusion** Age >50 Major elective non-cardiac procedures Hospital stay ≥2 days **Exclusion** N = Not described **Preoperative evaluation** -medical hx review -physical exam -functional status testing -cognitive status testing -laboratory tests **Testing instruments** Specific Activity Scale Telephone Interview for Cognitive Status (TICS) **Medication classes studied** Narcotics Benzodiazepines Anticholinergics **Preoperative Risk Factors independently associated with postoperative delirium (for matching controls)** Age Poor cognitive function Poor physical function Self-reported alcohol abuse Abnormal preop serum -sodium -potassium -glucose Aortic aneurism surgery Noncardiac thoracic surgery	**n = 91 developed delirium during post op days 2-5** Men and women (50%) Mean age 73 (8) Daily structured interviews by study personnel (days 2-5 postop; or day before discharge if before 6 days) -designed to test orientation and attention Mental status based on medical record (MEDICUS instrument) Medication exposures recorded for the 24 h before delirium developed	**Delirium assessment:** CAM MEDICUS **Baseline characteristics** **Primary outcomes (matched analysis)** Narcotics (class) Meperidine Morphine Fentanyl Oxycodone Codeine Epidural administration Meperidine (epidural) Fentanyl (epidural) Patient controlled administration Meperidine (PCA) Morphine (PCA) Benzodiazepines (class Long acting Short acting High Dose Low dose Anticholinergics (class) Diphenhydramine High dose Low dose	Delirium dx by meeting criteria on ≥1 day after the first postop day. CAM administered daily by trained study personnel post op days 2-5. In addition, altered mental status in both the medical record and in MEDICUS on the same day No significant differences between groups in preoperative risk factors **Delirium vs no delirium** **Differences between groups** **% vs %, OR (CI) (risk for delirium)** 95% vs 94%; 1.4 (0.5-4.3) 65% vs 42%; 2.7 (1.3-5.5) 24% vs 34%; 1.2 (0.6-2.4) 10% vs 9%; 1.5 (0.6-4.2) 10% vs 19%; 0.7 (0.3-1.6) 7% vs 7%; 1.1 (0.4-3.6) 64% vs 42%; 2.3 (1.2-4.4) 57% vs 34%; 2.4 (1.3-4.4) 5% vs 8%; 0.9 (0.3-2.7) 22% vs 32%; 1.1 (0.5-2.2) 4% vs 3%; 2.1 (0.4-10.7) 18% vs 29%; 0.9 (0.4-1.9) NOTE: p value not provided for narcotics 21% vs 8%; 3.0 (1.3-6.8), p <.01 7% vs 2%; 5.4 (1.0-29.2) *Long vs short* 14% vs 6%; 2.6 (1.1-6.5) *p = .02* 11% vs 3%; 3.3 (1.0-11.0) *High vs low* 10% vs 5%; 2.6 (0.8-9.1) *p = .03* 11% vs 8%; 1.5 (0.6-3.4), NS 10% vs 6%; 1.8 (0.7-4.5), NS 3% vs 3%; 1.5 (0.3-6.9), NS *high vs low* 8% vs 5%; 1.5 (0.5-4.1), NS *p = .66 NS*	**Medication exposure (all patients)** Narcotics = 94% Benzodiazepines = 13% Anticholinergics = 9% There was no interaction between the associations of drug exposure with delirium and the preoperative delirium risk scores. Postoperative exposures to meperidine and benzodiazepines were independently associated with the development of delirium within the next 24 hours. Although epidural analgesia was associated with delirium, it appears the association may be related to the use of meperidine in 85% of patients receiving epidural analgesia. The matched design of this study controlled for confounding by known preoperative risk factors for delirium and by studying only surgical patients, although neither of these eliminates all potential confounding . By limiting the exposure window to the 24-hour period before delirium developed, this study tried to eliminate medication exposures given in response to delirium.
		n = 154 no delirium (controls) 1 or 2 selected controls who did not have delirium matched for each case based on the same preoperative risk for delirium (if >2 patients matched, 2 randomly selected) Men and women (50%) Mean age 73 (8) Daily structured interviews (see above) Medication exposure (see above	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Secondary outcomes**	See above See above See above See above	
Conclusion: Clinicians caring for patients at risk for delirium should carefully evaluate the need for meperidine and benzodiazepines in the postoperative period and consider alternative therapies whenever possible.					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	NA – case control design
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	Unclear	NA – case control design
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	Unclear	Possible confounders (despite attempts to control for them)
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = Unclear**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 5**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G2-Taipale PG, Ratner PA, Galdas PM, et al. The association between nurse-administered midazolam following cardiac surgery and incident delirium: an observational study. Int J Nurs Stud. 2012;49(9):1064-73.

Study Characteristics	Population	Study Groups	Results		Comments
			Measure	Outcome	
Taipale PG 2012 Canada **Setting** tertiary care center **Study Design** Observational study **Selection method** Divided into 2 groups by whether have delirium **Study Length/Start-Stop Dates** 4/2009 to 10/ 2009 **Purpose** To examine the relationship between nurses' PRN administration of midazolam hydrochloride to cardiac surgery patients during the immediate post-operative period and the development of post-operative delirium. **Funding source(s):** Vancouver General Hospital School of Nursing Alumnae Association **Quality Score** 3 **Risk of Bias**: High	**N = 187 invited to participate** n = 33 refused or lost before consent N = 154 consented n = 32 excluded before surgery (see below) **N = 139 had surgery** n = 14 excluded due to exclusion criterion n = 1 withdrew n = 2 incomplete data **N = 122 analyzed** **Total sample:** Men and women (26.2%) Mean age 66.8 (9.4) **Inclusion** Cardiac surgery -CABG -aortic valve repair or replacement Cardiopulmonary bypass expected to be used during surgery Informed consent **Exclusion** N = see above Emergency surgery within 12 h of diagnosis Cognitive impairment (MMSE) Not English speaking Visual impairment Required hemodialysis preoperatively Hx substance misuse Self-reported alcohol use >7 drinks/week **All Patients Protocol:** Midazolam (0.5–2 mg every 6 min, PRN); median dose 3.0 mg -included in a set of physicians' standing orders -pre-printed and added to each patient's medical record. -nurses administered the drug following assessment of their patients' sedation levels and general status.	**n = 54 Liberal delirium group** Men and women (37.0%) Mean age 69.7 (8.3) "Liberal'' definition of delirium wherein patients were classified as having delirium if: (a) they had a physician's notation of delirium or (b) they had a positive CAM-ICU assessment and no mention of a physician's diagnosis **n = 68 Non-delirium group** Men and women (17.6%) Mean age 64.5 (9.6) See above	**Delirium assessment:** CAM-ICU **Baseline characteristics** Age Age Gender (male) **Baseline significant risk factors** Peripheral vascular disease P**rimary outcomes** CAM-ICU delirium Physician notes delirium CAM-ICU + physicians notes Midazolam dosages Midazolam increased delirium risk Conservative Liberal **Multivariate logistic regression risk factors** Conservative delirium Midazolam Age Liberal delirium Midazolam Age Peripheral vascular disease	MMSE performed before surgery. 4 trained study nurses administered CAM –ICU 12 to18 h after admission to ICU and daily post op. Medical records were reviewed. The ''conservative delirium'' required a physician's notes. Inter-rater reliability not determined; severity not discussed **Conservative classification** **Delirium vs no delirium** 69.2 (8.3%) vs 65.3 (9.7), p = .02 **Liberal delirium vs no delirium** 69.7 (8.3%) vs 64.5 (9.6%), p = .01 34 (63.0%) vs 56 (82.4%), p = .03 **Liberal delirium vs No-delirium** 12 (22.2) vs 4 (5.9) p = .02 27 (22.1%) 46 (37.7%) (conservative) 71.3% agreement 22.1% no midazolam 26.2% >6.0 mg OR (CI) 2.23 (1.06-4.70) 2.00 (0.96-4.13) **OR (95%CI), p** 1.08 (1.00–1.16), p=.04 1.05 (1.01–1.10), p=.03 1.07 (1.00–1.14), p=.06 (NS) 1.07 (1.02–1.12), p=.01 4.52 (1.31–15.59), p=. 02 NOTE: CAM-ICU may have identified some patients with the hypoactive form of delirium. Both approaches likely possessed some measurement error of unknown magnitude	The dosage of midazolam hydrochloride administered to cardiac patients is associated with the incidence of delirium independent of age and other risk factors. Few established risk factors for delirium were significantly associated with delirium in this sample. Limitations -sample size not achieved -inter-rater reliability of study nurses not determined -anesthetic and opiate agents administered in the operating room were not taken into account and may have influence sedation levels. The administration of midazolam should involve accurate assessments and explicit goals for sedation. Undesirable patient behavior should never be the rationale for extensive use of sedation.

Conclusion: Nurses play an important role in the prediction, assessment and prevention of post-operative delirium. Sedatives should be administered with caution because they increase a patient's risk of developing delirium. Sedatives should be administered with caution because they increase a patient's risk of developing delirium. Nurses' decisions regarding sedation administration must be informed by empirical knowledge, accurate assessment data and clear rationale with consideration of how these actions may contribute to the development of delirium.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	Significant differences in baseline data/risks
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	Observational study.
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	Observational study.
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	0	High	High % exclusions (post consent); dropouts
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Baseline imbalances Possible confounders noted by authors (see limitations above)
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 3**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G2-Luukkanen MJ, Uusvaara J, Laurila JV, et al. Anticholinergic drugs and their effects on delirium and mortality in the elderly. Dement Geriatr Cogn Dis Extra. 2011;1(1):43-50.

Study Characteristics	Population	Study Groups	Results		Comments
			Measure	Outcome	
Luukkanen MJ 2011 **Finland** **Setting** Multicenter 2 geriatric hospitals (7 acute wards) 7 nursing homes (13 wards) **Study Design** Cross-sectional **Selection method** Participants were divided into two groups according to their use of drugs with anticholinergic properties (DAPs): subjects receiving ≥ 2 DAPs and < 2 DAPs. **Study Length/Start-Stop Dates** Not described **Purpose** To investigate the use of drugs with anticholinergic properties (DAPs) and their associations with delirium and mortality among elderly patients with comorbidities. **Funding source(s):** Not disclosed **Quality Score** 3 **Risk of Bias**: High	**N = 425** n =. 230 acute geriatric wards n = 195 nursing home residents. n = 341 ≥ 2 DAPs n = 84 < 2 DAPs **Inclusion** >70 yrs Using DAPs on a regular basis **Exclusion** N = not described Age <70 Coma **Other assessment:** Mini-Mental State Examination (MMSE) Digit Span Clinical Dementia Rating (CDR) Wechsler Adult Intelligence Scale -proverb part (testing abstract thinking and judgment) Medical chart review by 2 investigators ADLs All medications **DAP lists in PDF** (see p 45) -high anticholinergic properties -detectable anticholinergic properties **Preexisting dementia** -global judgment of 3 geriatricians -existing dx -CDR Scale -nurse/caregiver interviews -CT/MRI imaging -previous MMSE scores	**n = 341 ≥ 2 DAPs** Men and women (83%) Mean age 86.7 (6.8) Primary school or less: 52.4% Widowed: 56.1 %	**Delirium assessment:** DSM-IV criteria **Baseline characteristics** Age Dependent in ADL Mean MMSE (SD) Mean number of medications Charlson Comorbidity Index Dementia Delirium by DSM-IV 2 Residence -Acute geriatric ward (n = 230) -Nursing home (n = 195) 2-year mortality dementia patients mortality **Primary outcomes** **Logistic regression** Use of DAPs predicts delirium	Trained geriatricians rated delirium based on cog test (MMSE, digital span, CDR) with diagnosis according to DSM-IV criteria. The criteria for delirium according to the DSM-IV were operationalized to simple yes/no questions and included in a questionnaire. **DAP user ≥2 vs DAP user <2** **Significant difference between groups** 86.7 (6.8) vs 83.7 (7.2), p<0.001 74.9 % vs 83.1%, p= 0.11 13.3 (7.9) vs 11.3 (7.6), p=0.045 8.9 (3.0) vs 6.1 (3.1), p <0.001 2.4 (1.6) vs 1.5 (1.2) , p<0.001 57.2 % vs 71.4%, p= 0.017 7.0 % vs 16.7%, p= 0.050 p=0.021 56.9% vs 43.1% 42.9% vs 57.1% 49.3% vs 35.7%, p=0.026 50.8% vs 31.7%, p=0.009 **Significant differences** OR 1.67, (0.87–3.2) (Adjusted for age, gender, and Charlson Comorbidity Index)	Over 80% of the patients in this study were using multiple DAPs as part of their everyday medication. DAP users were older and had more comorbid disease and they used more drugs than the non-users. Therefore, the higher prevalence of delirium and the worse prognosis among the DAP users compared with the non-users was expected. This study failed to show an independent prognostic significance for DAP use, The negative results should be interpreted with caution. -almost all subjects used at least 1 DAP -neither the short-term nor the long-term anticholinergic effect could be quantified in this setting - DAPs are only one of the precipitating factors for delirium and their influence may be masked by other triggers. -it is challenging to show an independent role for any single factor. . -the statistical power of the study may not be sufficient to show differences between the groups. The use of DAPs was more prevalent among patients without dementia compared to those with dementia. Limitations -cross-sectional design -confounding factors not controlled -variable anticholinergic properties of drugs rx
		n = 84 < 2 DAPs Men and women (76.2 %) Mean age 83.7 (7.2) Primary school or less: 52.2 % Widowed: 46.8%	**Risk factors** **Cox proportional hazard model:** Charlson Comorbidity Index Age Male gender Use of DAPs	 ***Independently associated with mortality*** HR 1.18, (1.08–1.29); p < 0.001 HR 1.06/year, (1.04–1.08); p< 0.001 HR 1.55, (1.09–2.20); p = 0.014 ***Not associated with mortality*** HR 1.12, (0.75–1.68); p = 0.56.	

Conclusion: We did not find a correlation between increased mortality or increased incidence of delirium with DAP treatment. Because the use of DAPs is very frequent among frail inpatients with comorbidities, these medications should be used with caution and at a minimum dosage, especially in patients with comorbidities or dementia.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	Significant differences between groups
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	Cross-sectional study
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	Cross-sectional study
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	High	Specific numbers not described
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Cross-sectional study Funding not disclosed Likely confounders noted by authors
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 3**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G2-Gamberini M, Bolliger D, Lurati Buse GA, et al. Rivastigmine for the prevention of postoperative delirium in elderly patients undergoing elective cardiac surgery--a randomized controlled trial. Crit Care Med. 2009;37(5):1762-8.

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects
			Measure	Outcome	
Gamberini 2009 Switzerland **Setting** University Hospital **Study Design** Double-blind, randomized, placebo-controlled trial **Randomization method** performed by the hospital pharmacy using a computer-generated sequence in blocks of 20 **Study Length/Start-Stop Dates** first 6 days pos-op 2/2006 to 7/2007 **Purpose** Tested the hypothesis that prophylactic short-term administration of oral rivastigmine, a cholinesterase inhibitor, reduces the incidence of delirium in elderly patients **Funding source(s):** unrestricted research grant from Novartis Switzerland **Quality Score** 6 **Risk of Bias**: High	**N = 348 assessed** n = 228 excluded **N = 120 randomized** n = 59 rivastigmine n = 61 placebo **Inclusion** >65 yrs undergoing elective cardiac surgery **Exclusion** N =228 Did not meet inclusion criteria, n = 117 Refused to participate, n = 92 Other reasons, n = 19 **Excluded from analysis** n = 7 (assess-ment with CAM not possible) **Other assessment:** Mini-Mental State Examinations (MMSE) clock drawing tests (CDT) Simplified Acute Physiology Score (SAPS II)	**n = 59 rivastigmine 1.5 mg/dose** n = 0 lost to follow up n = 7 discontinued intervention n = 1 death n = 6 withdrew from study **N = 56 analyzed** n = 3 excluded from analysis (assess-ment with CAM not possible) Men 37 (66%) Mean age 74.1 (5.2) Coronary artery bypass grafting: 30 (54%) Participants received placebo or rivastigmine 1.5mg every 8 hrs, starting on the evening preceding the operation and continuing through the intra-op and peri-op until the evening of the 6th postoperative day, i.e., a total of 22 doses. Patients are usually transferred to the normal ward, 48 hours after their operation. After diagnosed delirium, rescue treatment consisting of haloperidol with or without lorazepam was started at doses according to clinical discretion .	**Delirium assessment:** Confusion Assessment Method (CAM) **Baseline characteristics** SAPS II MMSE CDT **Primary outcomes** Delirium incidence **Secondary outcomes** MMSE BL: d 2 CDT BL: d2 use of a rescue treatment - haloperidol - lorazepam duration of delirium hospital days days spent in the ICU.	Study nurses and RAs rated CAM daily based on cog testing (MMSE, CDT) days 1-6. Inter-rater reliability and delirium severity were not discussed. **Rivastigmine vs Placebo** **N = 56 vs 57** 40 (15–60) vs 34.5 (18–67) 28 (23–30) vs 28 (23–30) 6 (2–6) vs 6 (2–6) 18 vs 17, p= 0.8 1 (-3–16)) vs1 (-4–16, p= 1.0 0 (-1–6) vs 0 (-3–6). p=0.9 17/56 vs18 /57, p =0.9 35/56 vs 38/57, p =0.6 2.5 (1–5) vs 3 (1–6), p=0.3 13 (7–39) vs 13 (7–39), p=0.3 2 (2–7) vs 2 (2–6), p=0.9	**Placebo vs Rivastigmine** (No significant difference) Deatha 1 (2) vs 1 (2) Perioperative strokea 2 (3) vs 1 (2) Seizuresa 1 (2) vs 0 (0) Nausea 32 (52) vs 40 (68) Vomiting 24 (39) vs 27 (46) Anorexia 41 (67) vs 39 (66) Diarrhea 6 (10) vs 7 (12) Dyspepsia 5 (8) vs 4 (7) Abdominal pain 8 (13) vs 8 (14) Vertigo 24 (39) vs 28 (47) Headache 6 (10) vs 7 (12) Tremor 3 (5) vs 5 (8) Insomnia 24 (39) vs 33 (56) Rash 0 (0) vs 0 (0) Sweating 28 (46) vs 25 (42) Atrial fibrillation 26 (43) vs 22 (37) Life-threatening arrhythmia 3 (5) vs 3 (5) Pacemaker >1 day 24 (39) vs 15 (25) **Comments:** In this study, 56% of the patients complained of nausea and 42% suffered from postoperative vomiting even in placebo group. Therefore, transdermal application of rivastigmine could have been an advantage. However, at the time of the study transdermal rivastigmine was not available.
		n = 61 placebo n = 1 lost to follow up n = 7 discontinued intervention n = 1 death n = 6 withdrew from study **N = 57 analyzed** n = 4 excluded from analysis (assess-ment with CAM not possible) Men 40 (70%) Mean age 74.4 (5.9) Coronary artery bypass grafting: 29 (51%) **See above**	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Secondary outcomes**	See above	
Conclusion: This negative or, because of methodologic issues, possibly failed trial does not support short-term prophylactic administration of oral rivastigmine to prevent postoperative delirium in elderly patients undergoing elective cardiac surgery with cardiopulmonary bypass.					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	1	Low	
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	High	Drop out 30/120 (25%) Exclusions after randomization
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Drug company sponsorship
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 6**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G2 G4 Liptzin B, Laki A, Garb JL, et al. Donepezil in the prevention and treatment of post-surgical delirium. Am J Geriatr Psychiatry. 2005;13(12):1100-6.

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects
			Measure	Outcome	
Liptzin 2005 **USA** **Setting** In patient (academic medical center) **Study Design** RCT – double blind, placebo controlled **Randomization method** Randomized separately by a research pharmacist; subjects, investigators, research assistant, orthopedic nursing staff blinded to study drug condition **Study Length/Start-Stop Dates** 5/2000 to 4/2003 **Purpose** To determine whether donepezil would reduce the incidence or duration of postoperative delirium, as defined by DSM-IV and that donepezil would reduce hospital length of stay or the number of transfers to sub-acute, short term skilled nursing or rehabilitation facilities **Funding source(s):** Pfizer **Quality Score** 5 **Risk of Bias**: High	**N = 90 randomized** n = 10 dropouts -not operated -did not take study meds n = 39 donepezil n = 41 placebo **Inclusion** Age ≥ 50 Elective total knee or hip arthroplasty **Exclusion** N = 187 --Evidence of GERD --Sick sinus syndrome Additional 19 excluded --Younger than 50 --Taking donepezil --Previously intolerant to donepezil --Non-English speaking --Participating in another orthopedic study **All patients protocol**: Operations performed by 1 of 2 orthopedic surgeons Informed of study in outpatient office Sent letter to contact study coordinator 1038 patients contacted 732 did not follow up or refused to participate -concern about surgery -leery of side effects -relatives did not support participation 306 patients invited to half-day education session (2-3 weeks before surgery) -screening process -informed consent -randomization After enrollment -MMSE -Clock Drawing Test	**n = 39 5 mg donepezil** Men and women (64%) Mean age 66.8 (8.9), 52-81 --Donepezil/placebo administered with breakfast for 14 days before and 14 days after surgery --Subjects were in charge of their medication throughout their participation --Tracked study drug use on a case report form in the hospital and at home (forms reviewed by the research assistant) --Admitted 24h before surgery (preop assessment) --Delirium Symptom Interview --Confusion Assessment Method --DSM IV criteria --Delirium assessed east postop day (as above) --Called days 7 and 14 to assess new or residual symptoms of delirium (collateral source information nor required)	**Delirium assessment:** Delirium Symptom Interview Confusion Assessment Method DSM IV criteria **Baseline characteristics/measures** MMSE Clock Drawing Test **All outcomes (ITT analysis done)** Subdromal delirium Mean duration Delirium Mean duration Mean (SE), range LOS (days) Disposition to rehab Discontinued study drug after randomization	RAs did daily DSI and CAM. Based on this, co-investigator gave delirium rating based on DSN-IV criteria *Donepezil vs placebo* No significant differences Both groups cognitively intact Average 29/30 *Average 9/10* *Donepezil vs placebo* No significant differences between groups (NS) (p) 71.8% vs 65.8% (0.57) 1.71 d vs 2.04 d (0.28) 20.5% vs 17.11% (0.69) 1.0 d vs 1.3 d (0.12) 4.4 (0.13), 4-8 vs 4.2 (0.8) 4-7, (0.09) 72% vs 83%, (0.23) 28% vs 27% (0.89)	Not discussed
		n = 41 placebo Men and women (51%) Mean age 67.6 (8.6), 51-90 See above	**Delirium assessment:** See above		
		n = 948 non participating patients Men and women (65%)	**Significant differences between participating and non participating patients** Age	Participants vs nonparticipants 2.2y younger [67.2 (8.70 vs 69.4 (8.9), p 0.03 No other significant differences	

Comments: Although all randomized patients were included in the analysis, only 58 patients actually completed the study. Adherence to study medication was poor. More than 25% of both groups took less than the 28 days of the assigned drug. There were no significant differences between groups for the study completers. Even when symptoms of delirium appeared, they were relatively mild and brief.

Conclusion: This study does not answer the question as to acetylcholinesterase inhibitors might be useful in other populations with delirium or at higher risk of developing it. This could include patients with terminal cancer, hip fractures, urinary tract infections, and those undergoing coronary artery bypass grafting.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	1	Low	
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	High	Adherence poor Dropouts not described; very high (28% donepezil vs 27% placebo)
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Pfizer funded
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	0		<50 both arms; 25% dropouts after randomization
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 5**

Instructions on rating:

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  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G2-Marcantonio ER, Palihnich K, Appleton P, Davis RB. Pilot randomized trial of donepezil hydrochloride for delirium after hip fracture. J Am Geriatr Soc. 2011;59Suppl 2:S282-8

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects
			Measure	**Outcome**	
Marcantonio ER 2011 USA **Setting** Large academic medical center **Study Design** Pilot RCT: double-masked placebo-controlled **Randomization method** Permuted block scheme stratified on dementia **Study Length/Start-Stop Dates** 30 days 1/2007 to 8/2008 **Purpose** To determine whether donepezil hydrochloride can reduce the prevalence and severity of delirium among older patients undergoing hip fracture repair. **Funding source(s):** NIA R21 AG027549 K24 AG035075 **Quality Score** 5 **Risk of Bias**: Unclear	**N = 93 eligible for screen** **N = 60 approached for participation** n = 16 enrolled **Inclusion** >70 yrs Hip fracture English speaking Adequate hearing Informed consent (patient or proxy) **Exclusion** N = 44 44 refused -14 unwilling to take additional medication -7 unwilling to incur added burden of study -5 unwilling to participate in any research -4 specific concerns about donepezil -1 inability to contact caregiver for consent **Stratified design** Controlled for any effect donepezil might have on underlying dementia rather on delirium Dementia assessed from the medical record and Informant Questionnaire for Cognitive Decline **Protocol for all patients:** All hip fracture patients at our medical center are admitted to a geriatrics-orthopedics service, and therefore receive perioperative co-management by a clinical geriatrics team using our previously developed protocol **Follow-up assessments** All subjects were revaluated about delirium on each postoperative hospital day, and at 2, 4, and 6 weeks Ongoing adherence and safety monitoring	**n = 7 Donepezil group (5 mg)** n = 1 withdrawal (after week 2) Men and Women 5 (71%) Mean age 88.0 ± 5.2 **Intervention** Initiate the study drug the day before surgery if possible, or within 24 hours after surgery. (Placebo appeared identical to donepezil) The study drug was administered daily, unless adverse events supervened, for a total treatment course of 30 days. 5 mg/ day dose of donepezil throughout the duration of the trial. After discharge, the remaining 30-day supply of "study drug" was sent with the patient for continued administration by the post-acute facility or by the family. Study coordinator contacted post-acute providers to ensure continuity of study drug treatment; also verified at follow up patient interviews	**Delirium assessment:** CAM Memorial Delirium Assessment Scale (MDAS). Delirium Symptom Interview (DSI) **Baseline characteristics** Women Dementia ADL Score **Primary outcomes** Delirium Presence Hospital Interviews (more than one per subject) Week 2 Week 4 Week 6 **Secondary outcomes** Delirium Severity Hospital Discharge Week 2 Week 4 Week 6 Adherence Median % pills taken per days on protocol	Trained RA rated CAM daily based on cog test (MMSE, digital span). MDAS for delirium severity. **Donepezil vs Placebo** No significant difference except gender 71% vs 44% 3 (43%) vs 4 (44%) NS 13.3 ± 3.6 vs 12.8 ± 4.7 NS No significant difference between groups 7/11 (64%) vs 9/14 (64%) p=0.9 3/7 (43%) vs 3/7 (43%) p=1.0 1/6 (17%) vs 3/7 (43%) p=0.6 3/6 (50%) vs 3/6 (50%) p=1.0 No significant difference between groups 1.3 ± 2.5 vs 1.6 ± 5.2 p=0.9 −0.1 ± 2.3 vs −2.2 ± 4.9 p=0.6 −1.2 ± 3.5 vs −2.0 ± 6.4 p=0.6 −0.6 ± 2.6 vs −2.0 ± 7.5 p=1.0 >90% both groups	**Side Effects:** **Donepezil vs Placebo** Insomnia 5/7=71% vs 1/9=11% p=0.04 Diarrhea 3/7=43% vs 0/9 p=0.06 Nausea 2/7=29% vs 2/9=22% p=1.0 Vomiting 1/7=14% vs 1/9=11% p=1.0 Syncope 1/7=14% vs 0/9 p=0.4 Dizziness 0/7 vs 1/9=11% p=1.0 Anorexia 0/7 vs 1/9=11% p=1.0 Frequency of Urination 1/7=14% vs 0/9 p=0.4 Total Side Effects per Patient Median (min, max) 2 (1, 3) vs 0 (0, 3) p=0.02 Any Side Effects 7/7=100% vs 4/9=44% p=0.04 **Serious Adverse Events** **Donepezil vs Placebo** Total Number of Events Observed N=2 vs N=0 Number of Patients with SAE (%) 2/7=29% vs 0/9 p=0.2 Code Breaking Event: N=2 vs N=0 p=0.2 Drug Stopped Early N (%) 2 (29%) vs 3 (33%) p=1.0 **Comments:** This study has high ineligibility rates (nearly 2/3), and low enrollment rates (27%). The limitations are the small sample size and a very elderly population (average age in high 80's), which would be the population at greatest risk for delirium after hip fracture. The stratified randomization scheme achieved balance of pre-fracture dementia status.
		n = 9 placebo group n = 2 withdrawals after discharge n = 1 withdrawal after week 4 Men and Women 4 (44%) Mean age 87.0 ± 3.7 Intervention: See above	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Secondary outcomes**	See above	

Conclusion: Patients randomized to donepezil had no significant improvement in delirium presence or severity, but experienced more side effects. Overall, we did not find sufficient evidence from our pilot to warrant a definitive Phase III trial.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	Unclear	donepezil group had a higher proportion of women because of small sample
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	1	Low	
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	High	4/16 withdrawals during follow up
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	1	Low	All patients analyzed (ITT not specified)
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = Unclear**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	0		Total 16
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 5**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G2-Sampson EL, Raven PR, Ndhlovu PN, et al. A randomized, double-blind, placebo-controlled trial of donepezil hydrochloride (Aricept) for reducing the incidence of postoperative delirium after elective total hip replacement. Int J Geriatr Psychiatry. 2007;22(4):343-9.

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects Comments
			Measure	Outcome	
Sampson EL 2007 UK **Setting** University hospital **Study Design** RCT (double blind, placebo controlled, parallel group) **Randomization method** block randomized by the hospital pharmacy department in groups of six (1:1 drug/ placebo ratio) **Study Length/Start-Stop Dates** 10/2003 to 1/2004 4 days **Purpose** To assess methodological feasibility and the safety and efficacy of donepezil (DPZ) in preventing post-operative delirium after elective total hip replacement surgery in older people without pre-existing dementia. **Funding source(s):** Educational grant from Pfizer Eisai, UK **Quality Score** 5 **Risk of Bias**: High	**N = 71 assessed for eligibility** n = 21 excluded (see below) **N = 50 randomized** n = 14 Withdrawn after randomization n = 4 surgery canceled on medical grounds n = 10 withdrew consent N = 36 n = 3 loss of follow up **N = 33 analyzed** n = 19 donepezil n = 14 placebo **Inclusion** Age >50 Elective total hip replacement surgery Attending the preadmission assessment clinic Informed consent **Exclusion** N = 21 n = 17 refused to participate n = 4 withdrew consent MMSE <26 Sensory impairment Hypersensitivity to DPZ or piperidine derivatives Contraindications to DPZ	**n = 21 Donepezil 5 mg** n = 2 lost to follow up **n = 19 analyzed** Men and women (42.1%) Mean age 69.7 (8.4) MMSE 29.2 (1.4) Subjects received their first dose of study medication post-operatively upon return to the orthopedic ward following elective hip replacement, when they were able to tolerate sips of water. Subjects took 5mg of Donepezil or placebo every 24 h for 3 days. The total duration of treatment was 4 days. Pharmacy dispensed both DPZ and placebo throughout study; randomization codes remained concealed; all analysis done blind to randomization code	**Delirium assessment:** Delirium Symptom Interview (DSI) **Baseline characteristics** **Primary outcomes** incidence of delirium Incidence of delirium Relative risk (CI) **Secondary outcomes** Mean length of hospital stay (days) Difference in means Mean length of delirium (days) Difference in means	DSI was rated by physicians or a trained research nurse in the morning of pre op and 3 times daily (morning, midday and evening) post op. Both incidence and severity measured by DSI with high interrater reliability No significant difference between groups 7 (21.2%) all patients **Donepezil vs placebo** 2 (9.5%) vs 5 (35.7%) 0.29 (0.06-1.30) 9.9 (0.73) vs 12.1 (1.09), p=0.09 -2.19 (-0.39 to 4.78) 1.5 vs 1.8 -0.3 (-0.38 to 1.41), p=0.83	49 possible adverse events, but none of these were considered to be serious and DPZ was well tolerated in this patient population. **Donepezil vs placebo** Nausea 6 vs 6 p=0.50 Vomiting 3 vs 1 p=0.45 Diarrhea 3 vs 2 p=0.90 Insomnia 9 vs 10 p= 0.16 Dizziness 4 vs 1 p=0.27 Paresthesia 1 vs 1 p= 0.82 Pyrexia 1 vs 1 p=0.82 Subjects with 1 AE: 1 vs 2 p= 0.37 Subjects with 2 AE : 17 vs 11 p= 0.38 Mean (SD) no. of AE per subject 1.84 (0.50) vs 1.71 (0.61) p=0.51 **Comments:** There was no evidence that DPZ was harmful; the drug was well tolerated an no serious adverse effects were reported. The results suggest possible benefits of DPZ over place with regard to the risk of delirium and length of hospital stay. The lack of significant benefit seen in this study may be due to the relatively good general health of this study population who had been selected as fit enough to undergo elective surgery. Methodological issues -small sample size -method of defining delirium may have increased sensitivity at the expense of specificity -not adequately powered to determine whether DPZ reduces delirium severity
		n = 15 placebo n = 1 lost to follow up **n = 14 analyzed** Men and women (57.1%) Mean age 65.1 (11.1) MMSE 28.8 (1.1) Placebo identical in appearance to donepezil supplied by Pfizer Eisai UK	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Secondary outcomes**	See above See above See above See above	

Conclusion: The experimental paradigm was feasible and acceptable. Donepezil did not significantly reduce the incidence of delirium or length of hospital stay, however for both outcomes there was a consistent trend suggesting possible benefit.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	1	Low	
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	High	Withdrawn after randomization =14 Loss of follow up = 3 Total dropouts = 17 (34%)
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Funding and placebo provide by Pfizer Eisai No ITT analysis
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	0		Total sample: 36
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 5**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G2-Overshott R, Vernon M, Morris J, Burns A. Rivastigmine in the treatment of delirium in older people: a pilot study. Int Psychogeriatr. 2010;22(5):812-8.

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects Comments
			Measure	Outcome	
Overshott 2010 **UK** **Setting** Academic hospital **Study Design** double-blind, placebo-controlled randomized pilot study **Randomization method** by numbered treatment packets statisticians. **Study Length/Start-Stop Dates** 28 days **Purpose** To determine whether rivastigmine would be safe and helpful in the treatment of delirium. **Funding source(s):** University Hospital of South Manchester NHS Foundation NHS Trust. **Quality Score** 4 **Risk of Bias**: High	**N = 15** n = 2 withdrawn . **Inclusion** Dx With delirium (CAM） >65 yrs **Exclusion** N = 69 Renal disease= 20 Cardiac disease= 15 Too ill= 10 Severe chest disease= 8 Liver function tests= 6 Delirium resolved=3 Refusal= 3 On a cholinesterase inhibitor= 2 Transferred out of area= 1 Alcohol detox= 1	**n = 8 Rivastigmine group** n – 7 CAM negative for 3 consecutive days n = 1 withdrew consent when CAM negative for 2 consecutive days Men: 4 (50%) Mean age 84.3 (11.2) Received rivastigmine 1.5 mg once a day increasing to 1.5 mg twice a day after 7 days	**Delirium assessment:** CAM **Baseline characteristics** Known dementia Mean MMSE (SD)at entry to trial **Primary outcomes** Duration of delirium **Secondary outcomes** Number discharged Number CAM negative when left study Deaths during admission	Daily rating (CAM) based on MMSE by research nurse, repeated by RA. Psychiatry determined if there was a difference. Inter-rater reliability and delirium severity were not discussed. **Rivastigmine vs Placebo** No difference between groups n = 8 vs 7 3 vs 4, p = 0.62 8.6 (4.9) vs 7.4 (7.1), p =0.7 6.3 (5.7) vs 9.9 (14.6), p=0.5 8 vs 3, p=0.03 8 vs 3, p=0.03 0 vs 4, p=0.03	A patient in the placebo group suffered from nausea. Three patients in the placebo group needed additional psychotropic medication (either risperidone or chlorrmethiazole) because of behavioral disturbance. **Comments** The small number diagnosed with delirium may reflect that nurse informants who completed the CAM may have under-estimated the number and significance of symptoms of their patients, especially as the study was conducted on busy acute medical wards where the subtleties of the presentation of delirium (e.g. hypoalert delirium) may not be identified because of high patient turnover and high workload. The blinded researchers were very successful in identifying which patients were in which treatment group. This is unlikely to happen by chance. There was obviously some aspect of how patients progressed whilst in the trial which suggested to researchers which group the patient was in.
		n = 7 placebo group n = 3 CAM negative for 3 consecutive days n = 2 patients became too ill (both later died) n = 1 CAM positive for 28 days (later died) n = 1 withdrawn for protocol violation (medication noncompliance) Men: 4 (57%) Mean age 80.6 (8.5) identical placebo administered as above (two tablets/day after 7 days)	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Secondary outcomes**	See above See above See above See above	
Conclusion: The numbers of patients who screened positive for delirium was very small and as a result the sample size was too small to make any meaningful inferences about treatment of delirium. Despite the small numbers included in the study, there are some indicators that rivastigmine may be safe and effective in treating delirium.					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	1	Low	NOTE: see comments in regard to blinded researchers ability to identify group allocation
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	High	Withdrawals: 2/15 (13%)
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	0	High	Did not report length of admission and discharge destination.
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Tablets were supplied by Novartis Pharmaceuticals U.K. Limited. No ITT analysis
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	0		T Total sample: 15
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 4**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G4-van Eijk MM, Roes KC, Honing ML, et al. Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial. Lancet. 2010;376(9755):1829-37.

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects
			Measure	Outcome	
Van Eijk 2010 Netherlands **Setting** Multicenter 6 ICUs **Study Design** RCT - double-blind, placebo-controlled **Randomization method** The trial pharmacist generated the randomization sequence (1:1) by computer; stratified by study center (all investigators, patients and families blinded) **Study Length/Start-Stop Dates** 11/2008 to 1/ 2010 **Purpose** To establish the eff ect of the cholinesterase inhibitor rivastigmine on the duration of delirium in critically ill patients. **Funding source(s):** ZonMw, the Netherlands Brain Foundation, and Novartis **Quality Score** 4 **Risk of Bias**: High	**N = 648 had delirium** **n = 539 excluded (main study)** **N = 109 with delirium enrolled and randomized** **N = 104 included in ITT analysis** n=88 reached endpoint of end of delirium or discharge from hospital **n=75 completed 90 days of follow-up** **Inclusion** >18 yrs admitted to ICU delirium (CAM-ICU) stay in ICU > 48 h. **Exclusion** N = 539 146 diagnosis uncertain 141 no informed consent 65 renal replacement therapy 22 hepatic encephalopathy 15 unable to receive enteric drugs 11 bradycardia 139 other reasons 31 could not speak Dutch or English 22 expected to be in intensive care unit for <48 h 79 logistical problems 7 not specified **Evaluation after treatment:** Richmond agitation sedation scale (RASS) Sequential Organ Failure Assessment (SOFA) scores	**n = 55 Rivastigmine group** n = 1 withdrawn by family **n = 54 in ITT analysis** n = 12 died n = 42 end of delirium or discharge n = 6 died **n = 36 completed follow up (90 days)** Men: 38 (70%) Mean age: 68·0 (11·4) APACHE II score 20·3 (8·9) SOFA score 5·6 (2·3) Charlson comorbidity index 2·6 (2·3) 2·3 (2·3) Emergency admission to intensive care unit 46 (85%) Patients received an increasing dose of rivastigmine or placebo, starting at 0·75 mL (1·5 mg rivastigmine) twice daily and increasing in increments to 3 mL (6 mg rivastigmine) twice daily from day 10 onwards, as an adjunct to usual care based on haloperidol.	**Delirium assessment:** CAM-ICU or CAM Delirium Severity Index (DSI) **Baseline characteristics** No significant differences except Men Emergency admission **Primary outcomes** Delirium duration (days) Endpoint of end of delirium (n=35 vs n=34) Endpoint of hospital discharge (n=7 vs n=12) Endpoint of death (n=12 vs n=4) **Secondary outcomes** Median of mean DSI scores Comatose (RASS -4 or -5) Non-comatose (RASS -3 or higher) ICU LOS	Assessed daily by trained nurses with CAM-ICU, and confirmed by research nurse. Any doubts about the delirium diagnosis were resolved by a psychiatrist, geriatrician, or neurologist consult. DSI for delirium severity. **Rivastigmine (54) vs placebo (50)** 38 (70%) vs 29 (58%) 46 (85%) vs 32 (64%) *No significant differences* **NS** 5·0 (2·7–14·2) vs 3·0 (1·0–9·3) p= 0·06 **NS** 4·0 (2·0–16·0) vs 2·5 (1·0–5·8) p=0·06 **NS** 6·0 (3·5–11·5) vs 6·0 (3·0–21·5), p= 0·95 **NS** 9·5 (4·8–11·8) vs 8·0 (1·0–9·0) p= 0·29 *Significant differences only* 2.3 (2,.0-3.1) vs 2,.0 (1.8-2.5) p 0.004 69/659 (10%) vs 16/459 (3%) p <0.0001 590/659 (90%) vs 443/459 (97%) p <0.0001 15 (9-30) vs 8 (3-17) p <0.0001	The Data Safety and Monitoring Board (DSMB) recommended that the trial be halted after the 4th interim analysis and inclusion of 109 patients. Mortality during treatment with the study drug seemed to be higher in the rivastigmine group n = 12 (22%) vs the placebo group n = 4 (8%), p = 0.07 based on sequential testing. The HR for delirium duration associated with rivastigmine use was 0.72 (0.44-1,17) did not change after adjustment (0.77; 0.47-1.26) or in post hoc analysis 0.80 (0.51-1.14); and after adjustment 0.84 (0.53-1.32) Post hoc censored for discharge from hospital but not death) Mortality was evenly balanced between participating centers. Protocol specified analyses were not done because the trial ended early so the sample size was too small. **Comments:** Rivastigmine was associated with a more severe type of delirium, longer stay in the ICU and higher mortality than placebo.
		n = 54 Placebo group n = 4 withdrawn by family **n = 50 in ITT analysis** n = 4 died n = 46 end of delirium or discharge n = 7 died **n = 39 completed follow up (90 days)** Men: 29 (58%) Mean age: 70·0 (12·2) APACHE II score 19·6 (7·9) SOFA score 5·5 (3·1) Charlson comorbidity index 2·3 (2·3) Emergency admission to intensive care unit 32 (64%) Identical placebo protocol (as above) (placebo drug same color, smell, taste and viscosity as rivastigmine)	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Secondary outcomes**	See above See above See above See above	
Conclusion: Rivastigmine had no beneficial effect for treatment of delirium in critically ill patients, and might have increased mortality. These results, combined with the findings of previous studies, do not support the use of cholinesterase inhibitors to treat delirium in critically ill patients					

In this trial, the cholinesterase inhibitor **QUALITY / RISK OF BIAS RATING WORKSHEET**

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	Significant baseline differences between groups
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	1	Low	
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	High	Early termination of trial due to deaths (also >10% dropouts)
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	0	Unclear	Early termination of trial – follow up data not available
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Drug company sponsorship of study
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 4**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

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  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G4-Breitbart W, Marotta R, Platt MM, et al. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. Am J Psychiatry. 1996;153(2):231-7.

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects Comments
			Measure	Outcome	
Breitbart W 1996 **USA** **Setting** Large metropolitan Cancer Center **Study Design** RCT (double blind) **Randomization method** Hospital pharmacy conducted randomization; also identified study drug if significant adverse effects occurred **Study Length/Start-Stop Dates** 28 weeks **Purpose** To determine the safest and most effective pharmacotherapies for the management of the mental symptoms and behavioral disturbances associated with delirium in AIDs patients. **Funding source(s):** Not described **Quality Score** 3 **Risk of Bias**: Unclear	**N = 419 approached for participation** **N = 244 informed consent** **N = 30 developed delirium** Men and women (23%) Mean age 39.2 (8.8) (23-56) **Inclusion** AIDS-related medical problems Medically stable Informed consent (to delirium protocol if delirium developed) Delirium present during study period **Exclusion** N = 175 (no specific data) Hypersensitivity to neuroleptics Hypersensitivity to benzodiazepines Presence of neuroleptic malignant syndrome Concurrent treatment with neuroleptic drugs Seizure disorder Current systemic chemo-therapy Withdrawal syndrome Anticholinergic delirium Current or past dx -schizophrenia -schizoaffective disorder -bipolar disorder Participation would compromise obtaining needed medical treatment Delirium associated with terminal event Lacked capacity for informed consent **Assessments** Delirium Rating Scale (DRS) DSM III R MMSE (also used to guide ratings on delirium severity) Extrapyramidal Symptom Rating Scale (ESRS) Side Effects and Symptoms Checklist Mental Status Profile	**n = 11 haloperidol** Treatment group-specific demographics not described Treatment protocol established for each study drug. Dose level mg (1-9) for oral and intramuscular administration Table 1, p 233 in PDF	**Delirium assessment:** DSM III R Delirium Rating Scale MMSE **Baseline characteristics** **Primary outcomes** Mean dose first 24 h (mg) Average maintenance dose Average DRS baseline Average DRS day 2 Average DRS end of tx Main effect for time Significant decrease in DRS Baseline to day 2 No significant difference in DRS day 2 to end of tx	Trained research staff monitored study patients daily for signs of delirium. Medical and nursing staff also trained. If delirium was suspected the study coordinator and study psychiatrist performed a full assessment Each study drug treatment protocol initiated (blinded); patients evaluated hourly with DRS, MMSE and ESRS No significant difference between treatment groups **Haloperidol vs chlorpromazine vs lorazepam** 2.8 (2.4) vs50 (23.1) vs 3.0 (3,.6) 1.4 (1.2) vs 36.0 (18.4) vs 4.6 (4.7) 20.45 (3.45) vs 20.62 (3.88) vs 18.33 (2.58) 12.45 (5.87) vs 12.08 (6.50) vs 17.33 (4,18) 11.64 (6.10) vs 11.85 (6.74) vs 17.00 (4.98) F = 10.09, df=2,27, p<0.001 Main effect for drug NS (p<0.44) F = 27.50, df=1, 27, p<0.001 P<0.43 vs p<0.81 vs p<0.81	No significant difference -medical complications p<0.32 -severity of complications p<0.61 Deaths (within 8 days of protocol initiation) n = 2 haloperidol n = 2 chlorpromazine n = 1 lorazepam Deaths within 1 week after completing the protocol n = 3 chlorpromazine n = 1 lorazepam Extrapyramidal side effects = none -no effect for time, p<0.81 -drug by time interaction = trend, p<0.07 -increase in lorazepam group **Comments** This study confirmed the clinical efficacy of neuroleptic drugs in the amelioration of delirium symptoms in AIDS patients. In addition, lorazepam alone is not effective in the treatment of delirium in AIDS patients, The doses of neuroleptics required to manage delirium in AIDS patients may be considerably lower than many reported in clinical standards. There may be disease specific mechanisms that explain why patients with AIDS required low doses.
		n = 13 chlorpromazine Treatment protocol – see above Table 1, p 233 in PDF	**Delirium assessment:** **Primary outcomes** Significant decrease in DRS Baseline to day 2 MMSE baseline to day 2 MMSE baseline to end of tx	See above F=37.02, df=1, 27, p<0.001 MMSE improved only for chlorpromazine group F=13.99, df=1,27, p<0.001 F=4.68, df=1,27, p<0.04	
		n = 6 lorazepam Treatment protocol – see above Table 1, p 233 in PDF	**Delirium assessment** **Primary outcomes** No significant decrease in DRS Baseline to day 2 Treatment-limiting side effects	See above F=0.23, df=1,27, p<0.63 All 6 patients developed side effects -increased confusion -oversedation -disinhibition -ataxia Lorazepam treatment discontinued Subsequent patients randomized to haloperidol or chlorpromazine	

Conclusion: Symptoms of delirium in medically hospitalized AIDS patients may be treated efficaciously with few side effects by using low-dose neuroleptics (haloperidol or chlorpromazine). Lorazepam alone appears to be ineffective and associated with treatment-limiting adverse effects.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	Unclear	Baseline date not reported except for age and gender of 30 patients with delirium
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	Unclear	Not clear whether outcome assessors were blinded
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	Unclear	Total patients approached and number consented, but no specific data on exclusions
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	All patients analyzed, but ITT protocol not performed Funding not disclosed
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = Unclear**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	0		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 3**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G2-Marcantonio ER, Juarez G, Goldman L, et al. The relationship of postoperative delirium with psychoactive medications. JAMA 1994;272(19):1518-1522.

Study Characteristics	Population	Study Groups	Results		Comments
			Measure	**Outcome**	
Marcantonio ER 1994 USA **Setting** University Hospital (General, Orthopedic and Gynecologic Surgery Depts) **Study Design** Prospective cohort (nested case control **Selection method** Cases and controls derived from a prospective cohort study of patients consenting to preoperative evaluation **Study Length/Start-Stop Dates** 11/1990-3/2002 **Purpose** To determine whether post-operative exposures to certain medications were independently associated with delirium, after controlling for pre-operative risk **Funding source(s):** Grant funding -Agency for Health Care Policy and Research -National Research Service Award for Research in Primary Care Medicine -Established Investigator Award (AHA) **Quality Score** 5 **Risk of Bias**: Unclear	**N = 1341 in prospective cohort** **N = 245 delirium +no delirium** n = 91 delirium n = 154 no delirium **Inclusion** Age >50 Major elective non-cardiac procedures Hospital stay ≥2 days **Exclusion** N = Not described **Preoperative evaluation** -medical hx review -physical exam -functional status testing -cognitive status testing -laboratory tests **Testing instruments** Specific Activity Scale Telephone Interview for Cognitive Status (TICS) **Medication classes studied** Narcotics Benzodiazepines Anticholinergics **Preoperative Risk Factors independently associated with postoperative delirium (for matching controls)** Age Poor cognitive function Poor physical function Self-reported alcohol abuse Abnormal preop serum -sodium -potassium -glucose Aortic aneurism surgery Noncardiac thoracic surgery	**n = 91 developed delirium during post op days 2-5** Men and women (50%) Mean age 73 (8) Daily structured interviews by study personnel (days 2-5 postop; or day before discharge if before 6 days) -designed to test orientation and attention Mental status based on medical record (MEDICUS instrument) Medication exposures recorded for the 24 h before delirium developed	**Delirium assessment:** CAM MEDICUS **Baseline characteristics** **Primary outcomes (matched analysis)** Narcotics (class) Meperidine Morphine Fentanyl Oxycodone Codeine Epidural administration Meperidine (epidural) Fentanyl (epidural) Patient controlled administration Meperidine (PCA) Morphine (PCA) Benzodiazepines (class Long acting Short acting High Dose Low dose Anticholinergics (class) Diphenhydramine High dose Low dose	Delirium dx by meeting criteria on ≥1 day after the first postop day. CAM administered daily by trained study personnel post op days 2-5. In addition, altered mental status in both the medical record and in MEDICUS on the same day No significant differences between groups in preoperative risk factors **Delirium vs no delirium** **Differences between groups** **% vs %, OR (CI) (risk for delirium)** 95% vs 94%; 1.4 (0.5-4.3) 65% vs 42%; 2.7 (1.3-5.5) 24% vs 34%; 1.2 (0.6-2.4) 10% vs 9%; 1.5 (0.6-4.2) 10% vs 19%; 0.7 (0.3-1.6) 7% vs 7%; 1.1 (0.4-3.6) 64% vs 42%; 2.3 (1.2-4.4) 57% vs 34%; 2.4 (1.3-4.4) 5% vs 8%; 0.9 (0.3-2.7) 22% vs 32%; 1.1 (0.5-2.2) 4% vs 3%; 2.1 (0.4-10.7) 18% vs 29%; 0.9 (0.4-1.9) NOTE: p value not provided for narcotics 21% vs 8%; 3.0 (1.3-6.8), p <.01 7% vs 2%; 5.4 (1.0-29.2) *Long vs short* 14% vs 6%; 2.6 (1.1-6.5) *p = .02* 11% vs 3%; 3.3 (1.0-11.0) *High vs low* 10% vs 5%; 2.6 (0.8-9.1) *p = .03* 11% vs 8%; 1.5 (0.6-3.4), NS 10% vs 6%; 1.8 (0.7-4.5), NS 3% vs 3%; 1.5 (0.3-6.9), NS *high vs low* 8% vs 5%; 1.5 (0.5-4.1), NS *p = .66 NS*	**Medication exposure (all patients)** Narcotics = 94% Benzodiazepines = 13% Anticholinergics = 9% There was no interaction between the associations of drug exposure with delirium and the preoperative delirium risk scores. Postoperative exposures to meperidine and benzodiazepines were independently associated with the development of delirium within the next 24 hours. Although epidural analgesia was associated with delirium, it appears the association may be related to the use of meperidine in 85% of patients receiving epidural analgesia. The matched design of this study controlled for confounding by known preoperative risk factors for delirium and by studying only surgical patients, although neither of these eliminates all potential confounding . By limiting the exposure window to the 24-hour period before delirium developed, this study tried to eliminate medication exposures given in response to delirium.
		n = 154 no delirium (controls) 1 or 2 selected controls who did not have delirium matched for each case based on the same preoperative risk for delirium (if >2 patients matched, 2 randomly selected) Men and women (50%) Mean age 73 (8) Daily structured interviews (see above) Medication exposure (see above	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Secondary outcomes**	See above See above See above See above	
Conclusion: Clinicians caring for patients at risk for delirium should carefully evaluate the need for meperidine and benzodiazepines in the postoperative period and consider alternative therapies whenever possible.					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	NA – case control design
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	Unclear	NA – case control design
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	Unclear	Possible confounders (despite attempts to control for them)
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = Unclear**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 5**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G4-Pisani MA, Murphy TE, Araujo KL,,et al. Benzodiazepine and opioid use and the duration of intensive care unit delirium in an older population. Crit Care Med. 2009;37(1):177-83.

Study Characteristics	Population	Intervention	Results		Adverse Effects Comments
			Measure	Outcome	
Pisani 2009 **USA** **Setting** Intensive care unit in an urban university teaching hospital. **Study Design** Prospective cohort study **Selection method** Consecutive admissions to medical ICU **Study Length/Start-Stop Dates** 9/5/ 2002 – 9/30/2004 **Purpose** To examine the impact of benzodiazepine or opioid use on the duration of ICU delirium in an older medical population. **Funding source(s):** CG-002-N, P30AG21342 NIH K23 (K23 AG 23023-01A1). #R21AG025193 , #K24AG000949 from NIA **Quality Score** 5 **Risk of Bias**: High	**N = 725 screened** **n = 318 eligible** n = 309 enrolled n = 5 excluded due to persistent stupor or coma **Study N = 304** Men (%) 143 (47%) Mean age 75 (8) Dementia: 94 (31%) Hx depression 85 (28%) Alcohol use: 120 (40%) ADL disability: 110 (36%) IADL disability: 260 (86%) Charlson Index: 1.8 (1.9) Benzodiazepines or opioids on admission: 75 (25%) Full code status on ICU admission 260 (86%) Body mass index: 25.8 **Inclusion** >60 yrs admitted to ICU **Exclusion** N = 416 193 admission <24 hr 83 transfer from another ICU 52 inability to communicate before admission 56 no identifiable proxy 23 non-English speaking 8 proxy refusals 1 patient refusal. **Data sources** Proxy interviews Medical records Prospective data collection after admission to ICU	**Other assessment:** short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCDE) Katz Activities of Daily Living Scale (ADL) Lawton's Instrumental Activities of Daily Living Scale (IADL) Charlson Comorbidity Index Acute Physiology and Chronic Health Evaluation Status score (APCHE II) **Drug data for the study population (n=304)** Benzodiazepine or opioid use: 247 (81%) Medium to high potency anticholinergic medication use: 98 (32%) Haloperidol use at any point during the ICU stay:97 (32%) Steroid use at any point during the ICU stay: 158 (52%)	**Delirium assessment:** Confusion Assessment Method-ICU (CAM-ICU) **Baseline characteristics** **ICU delirium data** Patients with delirium Dementia and delirium Patients with dementia, delirium and agitation No dementia and delirium No dementia, delirium and agitation First episode of ICU delirium (days, mean (SD) First episode of ICU delirium (days, median, range) Delirium on day of ICU discharge **Bivariate analysis for delirium duration outcome:** Benzodiazepine or opioid use Haloperidol use Impairment in ADL History of depression Dementia (IQCDE) APACHE II minus Glasgow Intubated Restraint use **Multivariable models for delirium duration** Benzodiazepine or opioid use [1] Control for dementia Control for haloperidol Control for APACHEII minus Glasgow Effect of benzodiazepines or opioids when dementia is absent [2] Effect of haloperidol when dementia is absent [3] 1: controlling for dementia, use of haloperidol, and baseline health status 2: Controlling for use of haloperidol and baseline health status 3. Controlling for use of opioids or benzodiazepines and baseline health status	Trained research nurses rated CAM-ICU based on cog test Monday through Friday. Inter-rater reliability was 100% CAM ICU supplemented by daily validated chart review method . N = 304 239 (79%) 89 (37%) 26 (29%) 148 (62%) 57 (38%) 4.7 (5.8) 3 (1-33) 83 (27%) **N=304 RR (LR), p** (significant results) 1.89 (31.49) p<0.001 1.42 (43.71) p<0.001 1.15 (6.40) p=0.01 1.15 (6.04) p=0.01 1.21 (11.24) p<0.001 1.01 (4.76) p = 0.03 1.81 (67.34) p<0.001 1.94 (95.22) p<0.001 **N = 304 RR (CI), p** (significant results) 1.64 (1.27–2.10), p <0.001 1.19 (1.07-1.33), p = 0.002 1.35 (1.21-1.50), p <0.001 1.01 (1.00-1.02) p = 0.02 2.42 (1.65–3.55), p <0.001 1.47 (1.29–1.69), p <0.001	Adverse Effects were not discussed. **Comments** The author did not examine benzodiazepines and opioids separately because only 28 participants received a benzodiazepine exclusively, 32 received an opioid exclusively, and all 21 receiving propofol also received a benzodiazepine and opioid. The author reviewed receipt of haloperidol and sedation status in the cohort and found that the majority of patients had delirium and 70% had agitation on the first day they received haloperidol. However, the author does not have documentation on what prompted prescription of haloperidol to the patients. The major innovation of the study is its examination of duration of delirium rather than occurrence. This is advantageous in an ICU study because so many patients have delirium on the first day of their ICU stay. A second strength is the firm establishment of a temporal ordering between receipt of medications and delirium to ensure their receipt before or concomitant with the first episode of delirium.

Conclusion: The use of benzodiazepines or opioids in the ICU is associated with longer duration of a first episode of delirium. Receipt of these medications may represent modifiable risk factors for delirium. Clinicians caring for ICU patients should carefully evaluate the need for benzodiazepines, opioids, and haloperidol.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	Observational study (one group)
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	Observational study (one group)
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	Observational study (one group)
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	1	Low	
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 5**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G4-Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology. 2006;104(1):21-6.

Study Characteristics	Population	Study Components	Results		Adverse Effects Comments
			Measure	Outcome	
Pandharipande P 2006 **USA** **Setting** University Medical Center **Study Design** Prospective cohort **Selection method** Consecutive patients meeting inclusion criteria **Study Length/Start-Stop Dates** 2/2000 – 5/2001 **Purpose** To study the temporal relation between time of administration of sedatives/analgesics and development of delirium and differentiate whether sedatives/analgesics were administered to treat the delirium or whether exposure to these agents resulted in delirium. **Funding source(s):** Not described **Quality Score** 3 **Risk of Bias**: High	**N = 275 consecutive patients** n = 77 excluded (see below) **N = 198 analyzed** n = 696 observations Men and women (48%) Mean age 55.5 (17.0) Charlson Comorbidity Index 3.6 (2.8) Vision deficits 114 (56%) Hearing deficits 32 (16%) Dementia score 0.2 (0.7) ADLs 0.9 (2.3) APACHE II 25.7 (8.4) SOFA 10.0 (3.3) Admission dx (>11%) -Sepsis/ARDS 47% -Pneumonia 19% -Other 29% **Inclusion** Any adult Mechanically ventilated Admission to medical or coronary ICU Informed consent from patient or surrogate **Exclusion** N = 77 51 = persistent coma 26 = lack of 2 consecutive cognitive assessments NOTE detailed description of Inclusion/Exclusion provided in previous papers (Ely et al 2001; Milbrandt et al 2004; Ely et al 2004; Ely et al 2003; See references #8, 9, 14, 15) **Assessments** Richmond Agitation Sedation Scale (RASS) Geriatric Depression Scale (GDS) Blessed Dementia Rating Scale (dementia score) Katz Activities of Daily Living (ADLs) Acute Physiology and Chronic Health Evaluation II (APACHE II) Sequential Organ Failure Assessment (SOFA	Sedative and analgesic medications prescribed according to a protocol adapted from the guidelines of the Society of Critical Care Medicine Medications titrated by bedside nurses to achieve -a target sedation level determined by the treating time using RASS -pain level using a behavioral pain indicator scale developed by the medical ICU Analgesics -morphine -fentanlyl Sedatives -lorazepam -propofol -midazolam Risk factors -age -visual and hearing deficits -history of dementia -depression (GDS) -severity of illness (modified APACHE II – removing the Glasgow Coma Scale) -sepsis -history of neurologic disease -baseline hematocrit -daily serum glucose concentrations	**Delirium assessment:** CAM-ICU RASS **Baseline characteristics** **Primary outcomes** Total observations Risk for transitioning to delirium Lorazepam Midazolam Fentanyl Morphine Propofol Lorazepam dose (Fig 1) Drug-drug interaction (lorazepam + each drug) Previous cognitive status Age >65 (Fig 2) Interaction lorazepam/age APACHE II (Fig 3) Antipsychotic exposure Delirium incidence Anticholinergic exposure Delirium incidence	Daily assessment using RASS and CAM-ICU (no detailed description) Single group; no comparison N = 198 696 included in analysis Multivariate analysis OR (CI), p 1.2 (1.1-1.4), 0.003 1.7 (0.9-3.2), 0.09 1.2 (1.0-1.5), 0.09 1.1 (0.9-1.2), 0.24 1.2 (0.9-1.7), 0.18 Incremental dose beyond 20 mg lorazepam in the preceding 24 h = 100% probability of transitioning to delirium (p = 0.003) None (all p values >0.05) None (did not modify contributory risk of these medications in transitioning to delirium) Probability increased for each year of life after 65 (p = 0.004) OR 1.02 (1.00-1.03), p = 0.04) None Probability increases for each additional point up to 18 then plateaus (0.004) OR 1.06 (1.02-1.11), p = 0.004 Administered to 75/198 (38%) 66/75 (88%) Not associated with transition to delirium (p = 0.39) Administered to 63/198 (32%) 52/63 (83%) Not associated with transition to delirium (p = 0.82)	Adverse effects not discussed **Comments** Every unit dose of lorazepam was associated with a higher risk of transitioning into delirium each subsequent 24-hour period even after adjusting for 11 relevant covariates. The use of opiates and sedatives (for the "double effect") which reduces the need for benzodiazepines or propofol may be prudent. Considering that delirium is a predictor of death and other adverse outcomes, investigators should consider prospective interventional studies to determine whether differing management strategies or selection of sedative/analgesic agents are associated with reductions in delirium and other short- and long-term clinical outcomes. Limitations -the list of covariates was not all-inclusive; excluding -renal/hepatic dysfunction -hypoxemia -sleep deprivation -more frequent delirium assessments would have allowed better tracking of cognitive status -used administered drug dose rather than plasma concentrations -excluded observations without accompanying assess-ments -only cursory evaluations of antipsychotics and anticholinergics
Conclusion: This study (using Markov regression modeling) documented that in addition to advancing age and APACHE II scores, there is an independent and dose-related temporal association between receiving lorazepam and transitioning to delirium, even after adjusting for relevant covariates.					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	Single group (no comparison)
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	NA – single group
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	NA – single group
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	Unclear	Observations excluded if no associated assessment(s) ?%
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Although multivariate analysis, limitations note possible confounding variables Funding not disclosed
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 3**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G4- Hakim SM, Othman AI, Naoum DO. Early treatment with risperidone for subsyndromal delirium after on-pump cardiac surgery in the elderly: a randomized trial. Anesthesiology. 2012;116(5):987-97.

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects
			Measure	**Outcome**	
Hakim 2012 **Egypt** **Setting** University hospital **Study Design** A randomized, double-blind, placebo-controlled, parallel-arm study **Randomization method** Randomization was carried out by a clinical pharmacist using a computer-generated random number list created with GraphPad StatMate v.1.01i software using permuted blocks of size 4. **Study Length/Start-Stop Dates** 12/2007 – 11/2010 **Purpose** To evaluate the effect of treating subsyndromal delirium (SSD) with risperidone on the incidence of clinical delirium in elderly patients who underwent on-pump cardiac surgery. **Funding source(s):** Support was provided solely from institutional and/or departmental sources. **Quality Score** = 8 **Risk of Bias**: Low	**N = 101** n = 51 intervention n = 50 **Inclusion** >65 yr Undergoing on-pump cardiac surgery No history of neuropsychiatric disorders, alcoholism, substance abuse, or intake of psychotropic medications. With SSD (ICDSC 1-3) **Exclusion** **N= 142** 19 Declined to participate 47 Not meeting inclusion criteria 76 Not meeting criteria for SSD **Exclusion criteria:** MMSE<25 GDS >4 Impaired hearing or visual acuity Speech difficulty Contraindication to risperidone or haloperidol Hx of neuroleptic malignant syndrome, Prolonged QTc syndrome Hx cerebrovascular disease other noncardiac procedures **Assessment of SSD:** Screening SSD using the Intensive Care Delirium Screening Checklist (ICDSC): physician who were trained systematically assessed 4 h after extubation and each 8-h nursing shift. Define SSD as ICDSC score of 1–3. **All patients protocol:** standardized balanced anesthetic technique, cardiopulmonary bypass, and a standard protocol was implemented for sedation, analgesia, and management of mechanical ventilation after surgery (see PDF).	**n = 51 risperidone 0.5 mg q12h po.** Men/women = 33/18 Age: 65 to 70 yr 36 (70.6%) >70 yr 15 (29.4%) **Intervention** The test drugs were continued for 24 h after subsidence of SSD (0 on the ICDSC) or until ICDSC >3. Patients who experienced delirium, the dose of risperidone was incrementally increased until symptoms were controlled or attained dose of 4 mg/d. **n = 50 placebo q12h po.** Men/women = 36/14 Age: 65 to 70 yr 39 (78%) >70 yr 11 (22%) **Intervention** (see above) Patients in the placebo group who experienced delirium were given 0.5 mg oral risperidone every 12 h, and if symptoms were not controlled, the dose could be increased to 4 mg/d. In either group, haloperidol was used as a second line rescue medication if symptoms were not controlled with risperidone in a daily dose of 4 mg. Haloperidol was begun orally at 0.5 mg q8h and could be escalated to 10 mg/d if needed. Rescue medications were started once the diagnosis of delirium was confirmed, and the dosage could be escalated by doubling the dose at 24-h intervals, if needed, until symptoms were controlled or the maximum dosage limit was attained. Rescue medications were continued for 24h after a score of 0 was achieved on the ICDSC.	**Delirium assessment:** Statistical Manual of Mental Disorders (DSM) **SSD assessment:** **Provide baseline zharacteristics/measures** Demographic and Pre-op Data - MMSE score (28-30) - MMSE score (25-27) -GDS (0-2) -GDS (3-4) Operative and Post-op Data -post-op intubation >24 h ICDSC score 1 ICDSC score 2 ICDSC score 3 **Primary outcomes:** Possibly delirious: ICDSC >3 Incidence of delirium (DSM) Absolute risk reduction Number needed to treat **Secondary outcomes:** Duration of delirium Need for haloperidol Highest doses of risperidone Highest doses haloperidol Highest score on the ICDSC Length of ICU LOS Extrapyramidal side effects **Adjusted analysis:** Failure to treat SSD with risperidone Rudolph Risk Score	If ICDSC >3, psychiatrist confirmed delirium using DSM criteria no inter-rater reliability, no cognitive testing done, no other details described. **See population column** ***Risperidone vs Placebo*** No significant difference 30 (58.8%) vs 31 (62%) 21 (41.2%) vs 19 (38%) 25 (49%) vs 26 (52%) 26 (51%) vs 24 (48%) No significant difference 5 (9.8%) vs 3 (6%) 19 (37.3%) vs 17 (34%) 17 (33.3%) vs 17 (34%) 15 (29.4%) vs 16 (32%) 8 (15.7%) vs 19 (38%), p =.011 7 (13.7%) vs 17 (34%), p =.031 0.20 (95% CI, 0.04 – 0.37) 4.9 (95% CI, 2.7–24.4) 3 (2 to 4) vs 3 (3 to 4) p=.664 2 (28.6%) vs 3 (17.6%) p=.608 3 (2 to 4) vs 3 (2.25 to 3.5) p=.318 0 (0 to 1.5) vs 0 (0 to 0) p=.757 6 (5 to 7) vs 5 (4 to 5) p=.234 2 (2 to 3) vs 3 (2 to 3) p=.517 6 (5 to 7) vs 6 (5 to 8) p=.056 2 (3.9%) vs 1 (2%) p=1.0 3.83 (95% CI, 1.63– 8.98; P=.002) 2.62 (95% CI, 1.51– 4.53; P=.001)	*Risperidone vs Placebo* **Extrapyramidal:** 2 (3.9%) vs 1 (2%); P=1.0 **Death:** 2 (3.9%) vs 1 (2%) **Mechanical ventilation:** 3 (5.9%) vs 2 (4%) **Second operation:** 1 (1.96%) vs 2 (4%) **Abnormality of the QTc interval and emergency breaking of the concealment envelopes** 0 vs 0 **Comments:** The current study showed that 57.1% of patients experienced SSD after surgery. The incidence of clinical delirium observed in the current study was 23.8%. Neither the ICDSC nor the CAM-ICU has been validated for severity scoring of delirium, so the highest score on the ICDSC was reported in the current study as a measure of severity, taking advantage of the ordinal framework of this scale. it is probable that the study had low power to detect a statistically significant difference between the two groups with regard to ICU, hospital length of stay, duration of delirium, highest score on the ICDSC, or consumption of antipsychotic medications.
Conclusion: Using risperidone in elderly patients who experienced subsyndromal delirium after onpump cardiac surgery was associated with significantly lower incidence of delirium.					

QUALITY / RISK OF BIAS

RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score** **1 or 0 [include notes for any 0s]**	**Risk of Bias Rating** **(Low; Unclear, High)** **[include notes on interpretation]**	**Notes for** **0 Quality Scores and** **Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	1	Low	
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study o For observational studies: confounders inadequately controlled o For RCT, lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	1	Low	Based on the intention to treat.
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = Low**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 8**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G4-Girard TD, Pandharipande PP, Carson SS, et al. .Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: the MIND randomized, placebo-controlled trial. Crit Care Med. 2010;38(2):428-37.

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects
			Measure	Outcome	
Girard 2010 **USA** **Setting** Multicenter – 6 tertiary care medical centers **Study Design** Randomized, double-blind, placebo-controlled trial. **Randomization method** Computer-generated, permuted block randomization scheme stratified according to study center. **Study Length/Start-Stop Dates** 21-day study period 2/2005 – 7/2007 **Purpose** To demonstrate the feasibility of a placebo-controlled trial of antipsychotics for delirium in the intensive care unit and to test the hypothesis that antipsychotics would improve days alive without delirium or coma. **Funding source(s):** NIH HL007123, the Hartford Geriatrics Health Outcomes Research Scholars Award Program, the Vanderbilt Physician Scientist development Program, and GRECC. **Quality Score** 6 **Risk of Bias**: Unclear	**N = 103 randomized and analyzed** n = 35 haloperidol n = 30 ziprasidone n = 36 placebo **Inclusion** >18 yrs ICU patients had abnormal level of consciousness or were receiving sedative or analgesic medications **Exclusion** N =3194 1000 neurologic injury 536 high risk of VT 344 ventilated >60 hrs 190 had no gastric access 174 post-suicide attempt 108 used neuroleptics 107 severe dementia 44 post-liver transplant 19 pregnant 16 neuroleptic allergy 247 enrolled in other study 210 no informed consent **All patients protocol:** The second dose of study drug was administered 12 hrs after if QTc interval >500 msec; and then q6h. Study drug frequency was reduced to every 8 hrs when patients were two consecutive negative for CAM-ICU. Reduced to every 12 hrs when patients were delirium/coma-free on three consecutive assessments, and discontinued when patients were delirium/coma-free on four consecutive assessments. Blood was collected from each patient within 48 hrs of study drug initiation.	**n =35 haloperidol every 6 hrs x 14 days** n = 2 discontinued protocol n = 2 withdrew **n = 35 analyzed** Female, 15 (43%) Mean age 51 (35–59) 5 mg haloperidol (as a solution containing 1 mg/mL) **n = 30 ziprasidone every 6 hrs x 14 days** n = 0 discontinued/ withdrew **n = 30 analyzed** Female, 9 (30%) Mean age 54 (47–66) 40 mg ziprasidone (as a solution containing 8 mg/mL) **n =36 placebo every 6 hrs x 14 days** n = 2 discontinued n = 1 withdrew n = 1 received EoL care **n = 36 analyzed** Female, 14 (39%) Mean age 56 (43–68) placebo (as a 5-mL solution)	**Delirium assessment:** Confusion Assessment Method for the ICU (CAM-ICU) RASS **Baseline measures** APACHE II score Brain dysfunction -Delirium -Coma Haloperidol before enrollment Ziprasidone before enrollment **Primary outcomes** Delirium/coma-free days **Secondary outcomes** ventilator-free days hospital length of stay 21-day mortality Average extrapyramidal symptoms score Daily delirium risk Study drug delivery and other antipsychotics	CAM-ICU rated by trained RAs twice daily based on RASS. Inter-rater reliability was not discussed. **Haloperidol vs ziprasidone vs Placebo** No significant difference between groups 26 vs 26 vs 26 16 vs 15 vs 17 12 vs 9 vs 14 1 vs 2 vs 4 0 vs 0 vs 0 **Haloperidol vs ziprasidone vs Placebo** 14.0 (6.0–18.0) vs 15.0 (9.1–18.0) vs 12.5 (1.2–17.2) 7.8 (0–15.0) vs 12.0 (0–18.6) vs 12.5 (0–23.3) (p =0.25), 13.8 vs 13.5 vs 15.4 (p =0.68) 4 vs 4 vs 6 (p = 0.81). 0 (0–0.2) vs 0 (0–0) vs 0 (0–0) p=0.56 **Haloperidol vs ziprasidone (OR (CI), p)** 1.2 (0.6 –2.2) vs 1.1 (0.5–2.2),p= 0.80 No significant difference	**Haloperidol vs ziprasidone vs Placebo** *Akathisia:* 10 (29%) vs 6 (20%) vs 7 (19%) (p =0 .60) *Extrapyramidal symptoms* similar between treatment groups (p =0.46). **Comments:** This pilot study was designed primarily to demonstrate the feasibility of a double-blind, placebo controlled trial of antipsychotics for ICU delirium, it was likely significantly underpowered to demonstrate the potential efficacy for many outcomes including length of stay and survival. Limitations of the trial include the small sample size, lack of enforcement by study personnel of a standardized sedation protocol, and the exposure of some patients in the ziprasidone and placebo groups to open-label haloperidol.

Conclusion: A randomized, placebo-controlled trial of antipsychotics for delirium in mechanically ventilated intensive care unit patients is feasible. Treatment with antipsychotics in this limited pilot trial did not improve the number of days alive without delirium or coma, nor did it increase adverse outcomes.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	1	Low	
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study o For observational studies: confounders inadequately controlled o For RCT, lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Sponsored by Pfizer, Inc., No ITT, but all randomized were analyzed
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = Unclear**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	0		Each group around 35
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 6**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G4-Breitbart W, Marotta R, Platt MM, et al. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. Am J Psychiatry. 1996;153(2):231-7.

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects Comments
			Measure	Outcome	
Breitbart W 1996 **USA** **Setting** Large metropolitan Cancer Center **Study Design** RCT (double blind) **Randomization method** Hospital pharmacy conducted randomization; also identified study drug if significant adverse effects occurred **Study Length/Start-Stop Dates** 28 weeks **Purpose** To determine the safest and most effective pharmacotherapies for the management of the mental symptoms and behavioral disturbances associated with delirium in AIDs patients. **Funding source(s):** Not described **Quality Score** 3 **Risk of Bias**: Unclear	**N = 419 approached for participation** **N = 244 informed consent** **N = 30 developed delirium** Men and women (23%) Mean age 39.2 (8.8) (23-56) **Inclusion** AIDS-related medical problems Medically stable Informed consent (to delirium protocol if delirium developed) Delirium present during study period **Exclusion** N = 175 (no specific data) Hypersensitivity to neuroleptics Hypersensitivity to benzodiazepines Presence of neuroleptic malignant syndrome Concurrent treatment with neuroleptic drugs Seizure disorder Current systemic chemo-therapy Withdrawal syndrome Anticholinergic delirium Current or past dx -schizophrenia -schizoaffective disorder -bipolar disorder Participation would compromise obtaining needed medical treatment Delirium associated with terminal event Lacked capacity for informed consent **Assessments** Delirium Rating Scale (DRS) DSM III R MMSE (also used to guide ratings on delirium severity) Extrapyramidal Symptom Rating Scale (ESRS) Side Effects and Symptoms Checklist Mental Status Profile	**n = 11 haloperidol** Treatment group-specific demographics not described Treatment protocol established for each study drug. Dose level mg (1-9) for oral and intramuscular administration Table 1, p 233 in PDF	**Delirium assessment:** DSM III R Delirium Rating Scale MMSE **Baseline characteristics** **Primary outcomes** Mean dose first 24 h (mg) Average maintenance dose Average DRS baseline Average DRS day 2 Average DRS end of tx Main effect for time Significant decrease in DRS Baseline to day 2 No significant difference in DRS day 2 to end of tx	Trained research staff monitored study patients daily for signs of delirium. Medical and nursing staff also trained. If delirium was suspected the study coordinator and study psychiatrist performed a full assessment Each study drug treatment protocol initiated (blinded); patients evaluated hourly with DRS, MMSE and ESRS No significant difference between treatment groups **Haloperidol vs chlorpromazine vs lorazepam** 2.8 (2.4) vs50 (23.1) vs 3.0 (3,.6) 1.4 (1.2) vs 36.0 (18.4) vs 4.6 (4.7) 20.45 (3.45) vs 20.62 (3.88) vs 18.33 (2.58) 12.45 (5.87) vs 12.08 (6.50) vs 17.33 (4,18) 11.64 (6.10) vs 11.85 (6.74) vs 17.00 (4.98) F = 10.09, df=2,27, p<0.001 Main effect for drug NS (p<0.44) F = 27.50, df=1, 27, p<0.001 P<0.43 vs p<0.81 vs p<0.81	No significant difference -medical complications p<0.32 -severity of complications p<0.61 Deaths (within 8 days of protocol initiation) n = 2 haloperidol n = 2 chlorpromazine n = 1 lorazepam Deaths within 1 week after completing the protocol n = 3 chlorpromazine n = 1 lorazepam Extrapyramidal side effects = none -no effect for time, p<0.81 -drug by time interaction = trend, p<0.07 -increase in lorazepam group **Comments** This study confirmed the clinical efficacy of neuroleptic drugs in the amelioration of delirium symptoms in AIDS patients. In addition, lorazepam alone is not effective in the treatment of delirium in AIDS patients, The doses of neuroleptics required to manage delirium in AIDS patients may be considerably lower than many reported in clinical standards. There may be disease specific mechanisms that explain why patients with AIDS required low doses.
		n = 13 chlorpromazine Treatment protocol – see above Table 1, p 233 in PDF	**Delirium assessment:** **Primary outcomes** Significant decrease in DRS Baseline to day 2 MMSE baseline to day 2 MMSE baseline to end of tx	See above F=37.02, df=1, 27, p<0.001 MMSE improved only for chlorpromazine group F=13.99, df=1,27, p<0.001 F=4.68, df=1,27, p<0.04	
		n = 6 lorazepam Treatment protocol – see above Table 1, p 233 in PDF	**Delirium assessment** **Primary outcomes** No significant decrease in DRS Baseline to day 2 Treatment-limiting side effects	See above F=0.23, df=1,27, p<0.63 All 6 patients developed side effects -increased confusion -oversedation -disinhibition -ataxia Lorazepam treatment discontinued Subsequent patients randomized to haloperidol or chlorpromazine	

Conclusion: Symptoms of delirium in medically hospitalized AIDS patients may be treated efficaciously with few side effects by using low-dose neuroleptics (haloperidol or chlorpromazine). Lorazepam alone appears to be ineffective and associated with treatment-limiting adverse effects.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	Unclear	Baseline date not reported except for age and gender of 30 patients with delirium
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	Unclear	Not clear whether outcome assessors were blinded
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	Unclear	Total patients approached and number consented, but no specific data on exclusions
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	All patients analyzed, but ITT protocol not performed Funding not disclosed
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = Unclear**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	0		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 3**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G3-G5-Lundstrom M, Edlund A, Karlsson S, et al. A multifactorial intervention program reduces the duration of delirium, length of hospitalization, and mortality in delirious patients. J Am Geriatr Soc. 2005;53(4):622-8.

Study Characteristics	Population	Intervention Groups	Results		Comments Conclusion
			Measure	Outcome	
Lundstrom M 2005 Sweden **Setting** Department of General Internal Medicine, University Hospital **Study Design** Prospective Controlled clinical trial **Selection method** Consecutive admission to 2 wards (intervention ward; control ward) Random allocation from ED based on available bed; readmissions within 3 months of discharge admitted to the same ward as previous treatment **Study Length/Start-Stop Dates** Not described **Purpose** To investigate whether an education program and a reorganization of nursing and medical care improved the outcome for older delirious patients. **Funding source(s):** Joint Committee of theNorthern Health Region of Sweden (Visare Norr), et al **Quality Score** 3 **Risk of Bias**: High	**N = 400** **Inclusion** Age ≥70 Informed consent **Exclusion** N = not described Age <70 Declined participation **Other assessment (all patients):** RA assessed on Days 1, 3, and 7 after admission Organic Brain Syndrome (OBS) Scale, MMSE Katz ADL index Vision testing (admission) Hearing testing (admission)	**n = 200 Intervention group** Men /women% 39.0/61.0 Mean age 79.4 (5.6) 1. A 2-day course for staff on geriatric medicine focusing on assessment, prevention, and treatment of delirium 2. Education concerning caregiver-patient interaction focusing on patients with dementia and delirium 3. Reorganization from a task-allocation care system to a patient-allocation system with individualized care 4. Guidance for nursing staff once a month No blinding	**Delirium assessment:** DSM-IV **Baseline characteristics** Age Male% vs Female % Diabetes mellitus Stroke % Myocardial infarction **Logistic Regression to Control for Baseline Differences** Ward Stroke on admission Sex Age Diabetes mellitus **Primary outcomes** Delirium incidence Delirium prevalence (24h) Delirium incidence (Day3) Delirium incidence (Day7) **Secondary outcomes** Length of stay(days) Return to home/apt *Delirious patients* Return to home/apt Mortality	Three of the authors rate OBS scale and MMSE on days 1,3, and 7, then determined delirium according to DSM-IV criteria (90% inter-rater agreement) (authors blinded to allocation) Significant difference between groups **Intervention vs control** 79,4 (5.6) vs 80,7 (6.2), p=.02 39.0%/ 61.0% vs 49.5%/50.5%, p=.04 42.5% vs 23.5% p<0.001 170% vs 25.0%, p=..05 10% vs 4.5%, p=.03 **Delirious Patients in the Two Wards (N=125; n = 63 vs n = 62))** OR=3.12 (1.43–6.81) OR=1.44 (0.62–3.35) OR=1.35 (0.59–3.05) OR=1.01 (0.95–1.08) OR=0.53 (0.22–1.27) **Day 1 vs Day 3** 123/400 (30.8%) vs 82/400 (20.5%),p <.001 **Intervention vs control** 31.5% vs 31.0%; p=.91 58.7% vs 72.6%; p=.10 30.2% vs 59.7%; p=.001 **Intervention vs control** 9.4 (8.2) vs 13.4 (2.3); p<.001 86.6% vs 82.4%; p=.29 78.3% vs 60%; p=.05 2 (3.2%) vs9 (14.5%); p=.03	Too few patients had dementia in the present study to allow analyses of patients with dementia separately, but no patient with dementia remained delirious on Day 7 in the intervention ward, compared with four patients still delirious on Day 7 in the control ward, which might indicate that delirium in patients with dementia can be successfully treated. Limitations -randomization/allocation dependent on bed availability -RA assessors not blinded -assessments not done daily -discharged patients regarded as not delirious on Day 7 (1 patient assessed as delirious within 24 h of discharge) **Conclusion** This study shows that a multifactorial intervention program reduces the duration of delirium, length of hospital stay, and mortality in delirious patients.
		n = 200 Control group Men/women % 49.5/50.5 Mean age 80.7 (6.2) Usual hospital care organized in a task-allocation care system; -the same caregiver handled particular tasks for all patients, -no clinical caregiver had full responsibility for an individual patient during his or her entire hospitalization. Staff aware that a screening of delirium prevalence was being performed	**Delirium assessment:** **Baseline characteristics/measures** **Primary outcomes** **Secondary outcomes**	See above	

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	Randomization based on bed availability; significant baseline differences between groups
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	Allocation concealed only for authors who determined delirium dx
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	No blinding except authors who determined delirium dx
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	High	No information on number of patients excluded
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	Unclear	Numerous baseline imbalances, but analyzed to determine OR related to delirious patients Unknown confounders possible because delirium assessment not done daily
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 3**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G3-Zaubler TS, Murphy K, Rizzuto L, et al. Quality improvement and cost savings with multicomponent delirium interventions: replication of the Hospital Elder Life Program in a community hospital. Psychosomatics. 2013;54(3):219-26.

Study Characteristics	Population	Intervention Groups	Results		Comments
			Measure	Outcome	
Zaubler TS 2013 **USA** **Setting** General medical floor at a community hospital **Study Design** Quality improvement study (Pre-Post design) **Selection method** Patients admitted to general medical floor **Study Length/Start-Stop Dates** 11/2010 – 2/2011 (pre) 7/2011 – 3/2012 (post) **Purpose** To implement an adapted HELP program in a community hospital and to prospectively assess its effectiveness and cost impact in this setting. **Funding source(s):** Grants from Head Charitable Foundation and the Marion E. C. Walls Trust **Quality Score** 3 **Risk of Bias**: High	**N = 595 enrolled** **Inclusion** -All patients age ≥ 70 -with or without delirium on admission NOTE: usual HELP requirement for 1 delirium risk factor other than age not implemented in this study **Exclusion** N = not discussed Not likely to benefit from the interventions -Non-verbal - terminal illness -refused to participate **All patients** Assessed with CAM Brief cognitive screen (not identified) Digit Span Test **Training** Volunteer recruitment (beginning 11/2010) Trained in HELP core interventions Supervised by Elder Life Specialists **Cost savings** Comparisons between delirium and no delirium patients Variable costs compared for patients with dx of pneumonia Potential increased revenue calculated based on LOS	**n = 380 Intervention** (7/2011-3/2012) Men and women (61%) Mean age 83.2 (6.6) **Protocol** -Patients received interventions from the Elder Life Specialists or volunteers, on weekdays, 5 days per week, adapted from the original HELP model -Exercise/mobility protocol was omitted because of staffing limitations Adapted HELP program interventions and activities -Daily visits -Therapeutic activities -Feeding assistance -Hydration assistance -Vision/hearing protocol -Sleep assistance	**Delirium assessment:** CAM **Baseline characteristics** **Primary outcomes** Delirium episodes Patient days w/ delirium All patients LOS(d) mean *LOS For non-delirious patients (n=506)* **Financial Outcomes** Savings (variable costs) Revenues (potential increase) Total	After screening assessment, CAM administered twice daily on weekdays (medical record reviewed for delirium on weekends and holidays) Elder Life Specialist usually administered CAM (description vague) No significant difference between groups **Pre-Intervention vs. Intervention** 20% vs. 12% p=0.019 129(8%) vs. 123(6%) p=0.005 7.4(6.4) vs. 5.2(4.2) p<0.001 7.2(6.2) vs. 5.0(4.1) p<0.001 **Study (9 months) / Annualized** $81,000 / $108,000 $760,000 / $1,014,000 $841, 000 / $ 1,112,000	Since it is exceedingly difficult in a community hospital setting to maintain HELP interventions more than 5 days per week, it was often impossible to discriminate between prevalent (pre-admission) and incident (arising after admission) delirium. The HELP interventions, therefore, were not limited to those without delirium at the time of the first assessment as was the case in other studies. Overall LOS among all patients enrolled in the intervention group decreased by 2 days. Interestingly, the LOS for patients without delirium had a highly significant 1-day reduction in LOS. This suggests that HELP benefits non-delirious patients, possibly by minimizing physical or cognitive decline during hospitalization and/or improved coordination of care and dis-charge planning with the inclusion of the Elder Life Specialists in clinical rounds. Another compelling outcome was the annual cost savings of $1,122,000. This more than offsets the cost of the salary of the two Elder Life Specialists and minimal sup plies that were purchased ($96,763). Limitations -assessments and interventions only on weekdays -difficult to discriminate between prevalent and incident delirium -no concurrent control group
		n = 215 Pre-intervention (11/2010-2/2011) Men and women (63%) Mean age 82.2(7.3) **Protocol** Usual care	**Delirium assessment:** **Baseline characteristics** **Primary outcomes**	See above See above See above	
Conclusion: HELP can be successfully adapted for implementation in a community hospital setting to decrease delirium episodes, total patient-days with delirium and LOS, and generate substantial cost savings.					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	Pre/post study design (no matching)
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	Pre/post study design
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	Pre/post study design; outcome assessors not blinded
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	Unclear	No detail on excluded patients
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Historical controls Pre/post design Intervention implemented only on weekdays
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 3**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
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  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G3-G5-Rubin FH, Williams JT, Lescisin DA, et al. Replicating the Hospital Elder Life Program in a community hospital and demonstrating effectiveness using quality improvement methodology. J Am Geriatr Soc. 2006;54(6):969-74

Study Characteristics	Population	Intervention Groups	Results		Comments
			Measure	Outcome	
RubinFH 2011 USA **Setting** Community teaching hospital **Study Design** Pre-test/post-test quality improvement study **Selection method** Patients admitted to a nursing unit **Study Length/Start-Stop Dates** 2001 - 2002 **Purpose** To evaluate a replication of the Hospital Elder Life Program (HELP), a quality-improvement model, in a community hospital without a research infrastructure, using administrative data **Funding source(s):** Shadyside Hospital Foundation funded the Shadyside replication. The HELP dissemination effort was funded in part by grants from the National Library of Medicine, the Commonwealth Fund the Fan Fox and Leslie R. Samuels Foundation), and the Retirement Research Foundation. **Quality Score**: 3 **Risk of Bias**: High	**N = 1929** n = 1225 baseline (pre-intervention) n = 704 post intervention **Inclusion** Aged ≥ 70 Admitted to Hospital Elder Life **Exclusion** N = not discussed -Diagnosis of schizophrenia -Baseline use of major tranquilizers **HELP Implementation personnel** -Elder life specialist (1.0 FTE) -clinical geriatrician (0.1 FTE) -geriatric nurse practitioner (0.5 FTE)	**n = 704 HELP Intervention** Time period: 7/2002 – 12/2002 Men and women (63.5%) Mean age 80.9 (6.7) Phase in data collected 1/2002 through 6/2002 HELP implementation 7/2002-12/2002 **Protocol** **Hospital Elder Life Program** Daily interventions targeted patients were not delirious and who were at intermediate risk for developing delirium Risk factors present: -cognitive impairment -sleep deprivation -immobility -visual or hearing impairment -dehydration Deviations from the original HELP model -exercise and fluid repletion protocols omitted due to insufficient staffing -sleep protocol modified -the Role of the nurse practitioner was modified to eliminate redundancies with existing services	**Delirium assessment:** Specific assessment tools not described **Baseline characteristics** Cerebrovascular disease Gastrointestinal disease Ischemic heart disease Renal failure **Primary outcomes** Delirium rates **Financial outcomes** Est 101 cases prevented 14.4% reduction in delirium rate Net cost savings (cost savings –cost of HELP) **Nursing satisfaction outcomes** Nurses and nurses' aides Agreed Highly agreed Patient satisfaction with HELP	A nurse practitioner evaluated patients for the presence of delirium and for the presence of modifiable predisposing or precipitating factors. She interacted with staff nurses and treating physiciabns. Significant difference between groups Baseline vs HELP 7.4% vs 3,7%, p .001 5.1% vs 12.4%, p <.001 2.7% vs 4.5%, p .04 0.4% vs 1.4%, p .03 **Baseline vs. Intervention** 40.8% vs. 26.4% p < .002 $220,281 cost savings 364 bed-days saved $562,611 in 6 mos on one 40-bed nursing unit "My job is more satisfying due to HELP" "It would be helpful to make HELP a permanent program on my unit" 2.8/3 rating for overall satisfaction	Factors contributing to success at Shadyside included -a long tradition of QI improvements for elderly inpatients; -inclusion of all stakeholders in the project, especially nursing and ancillary personnel, so that concerns of competition or ''turf'' were resolved at the outset; -an accompanying educational campaign to generate support; -an identified senior physician champion; -use of data that hospital leadership found credible; -agreement with management at the outset on what outcomes would be important; -beginning with only one unit; -institution-wide celebration of results.
		n = 1,225 Baseline (control) Time period: 1/2001 – 12/2001 Men and women (63.8%) Mean age 80.6 (6.2) Baseline data measured throughout 2001 **Protocol** Standard care	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Secondary outcomes**	See above See above See above See above	

Conclusion: **Conclusion**: HELP can be successfully replicated in a community hospital, yielding clinical and financial benefits

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	Individuals not randomized or individual matched. Differences between groups
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	Allocation not concealed due to different time periods
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	Outcome assessors not blinded
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Pre/post design Cohorts were assessed at different time periods and thus there may be other confounding variables
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	0		Delirium assessment tool not described
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 3**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G3-G5-Inouye SK. Prevention of delirium in hospitalized older patients: risk factors and targeted intervention strategies. Ann Med. 2000a;32(4):257-63.

Study Characteristics	Population	Studies	Results		Other information
			Measure	Outcome	
Inouye 2000a **USA** **Setting** General medicine service at a university hospital **Study Design** -prospective studies to examine predisposing and precipitating factors for delirium, -controlled clinical trial intervention using prospective individual matching **Selection method** Delirium Prevention Trial: consecutive patients admitted to general medicine service at university hospital **Study Length/Start-Stop Dates** Not discussed **Purpose** To describe the multifactorial etiology of delirium; to elucidate the predisposing and precipitating factors for delirium derived from earlier work; and to present an overview of the Delirium Prevention Trial, which was targeted to address delirium risk factors. **Funding source(s):** Grants from NIA and Patrick and Catherine Weldon Donaghue Medical Research Foundation **Quality Score**: 7 **Risk of Bias**: Unclear	**Delirium Prevention Trial** **N = 852 enrolled** n=426 matched pairs of intervention-control patients . **Inclusion** Age ≥ 70 -no evidence of delirium at admission -intermediate to high risk for delirium at baseline **Exclusion** Not discussed ****** **Delirium Prevention Trial** Prospective matching strategy to assure comparability of patients between intervention and control groups **Protocols for targeted risk factors** Cognitive impairment -reality orientation -therapeutic activities Sleep deprivation -noise reduction -uninterrupted slep Immobility -early mobilization -minimize immobilizing equipment Visual impairment -vision aids -adaptive equipment Hearing impairment -amplifying devices -hearing aids -wax disimpaction Dehydration -early recognition -volume repletion	*To identify predisposing factors for developing of delirium during hospitalization* **n = 107 patients first cohort** **n = 174 second cohort** **(validated first cohort findings)** **Inclusion** Age ≥ 70 -admitted to general medicine service at a university hospital	>30 potential risk factor variables studied **Predisposing risk factors** Vision impairments (acuity <20/70) Severe illness (APACHE II >16) Cognitive impairment (MMSE <24) Dehydration (BUN/CR ratio ≥ 18(	 RR 3.5 (1.2 – 10.7) RR 3.5 (1.5 – 8.2) RR 2.8 (1.2 – 6.7) RR 2.0 (0.9 – 4.6)	Patients placed in low (no factors present), intermediate (one or two factors present), or high (three or four factors present) risk groups showed a statistically significant trend towards increasing risk of delirium with increasing numbers of predisposing factors. RR for delirium increased from 1.0 in low-risk group to 9.2 in high-risk group. -predictive model and risk stratification system validated in the second cohort of patients
		Examine precipitating factors for delirium during hospitalization. Two prospective cohorts of consecutive patients aged 70 years and older admitted to general medical service **n = 196 first cohort** **n = 312 second cohort** **Inclusion** Age ≥ 70 -admitted to general medicine service at a university hospital	Develop and validate a predictive model for delirium based on noxious insults or factors occurring during hospitalization >25 candidate risk factor variables studied **Precipitating factors** Use of physical restraints Malnutrition More than 3 medications added Use of bladder catheter Any iatrogenic event	 RR 4.4 (2.5 – 7.9) RR 4.0 (2.2 – 7.4) RR 2.9 (1.6 – 5.4) RR 2.4 (1.2 – 4.7) RR 1.9 (1.1 – 3.2)	Study demonstrated distinct risk gradients, with patients placed in low, intermediate, or high-risk groups showing a statistically significant trend towards increasing risk of delirium with increasing numbers of precipitating factors. RR for delirium increased from 1.0 in the low-risk group to 22.7 in the high-risk group. -validated in the second cohort of patients which produced similar, statistically significant risk gradients.
		Intervention group = 426 **Delirium Prevention Trial Intervention (Hospital Elder Life Protocol)** **Intervention (see Protocols for targeted risk factors)** Standardized protocols targeted towards six delirium risk factors. **Delirium assessment: Assessment tool: CAM** All patients assessed daily by RAs who had no role in the intervention unaware of intervention or study group assignment **Control Group = 426** Protocol = Usual care with daily delirium assessment	Incidence of delirium Days of delirium Total no. episodes of delirium Rate of adherence to all intervention protocols Adherence rate for individual intervention protocols Intervention resulted in a significant reduction in the total number of risk factors per patient compared with the usual care group at reassessment Improvement in the orientation score of patients with cognitive impairment at admission Reduction in the rate of use of sleep medications in all patients	**Intervention vs. control** 9.9% vs. 15% OR .6 (0.39-.92) 105 vs. 161 p = 0.02 62. vs., 90 p = 0.03 87% 71% - 96% p = 0.001 40% vs 26% improved; p = 0.04 46% vs 35%; p = 0.001 NOTE: Specific recommendations for delirium prevention detailed in PDF	No adverse effects were associated with any intervention protocols Through the identification of risk factors and targeting intervention strategies towards them, we have been successful in preventing delirium in hospitalized older patients, reducing the risk of delirium by 40%. Results suggest that primary prevention of delirium, (preventing delirium before it occurs), may be the most effective treatment strategy for delirium, a finding which holds substantial clinical and health policy implications for delirium management in specific and for the geriatric population more generally.
Conclusion: Through the identification of risk factors and targeting intervention strategies towards them, we have been successful in preventing delirium in hospitalized older patients, reducing the risk of delirium by 40%.					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	Unclear	Not discussed
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	1	Low	
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = Unclear**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 7**

Instructions on rating:

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  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G3-G5-Lundstrom M, Olofsson B, Stenvall M, et al. Postoperative delirium in old patients with femoral neck fracture: a randomized intervention study. Aging Clin Exp Res. 2007;19(3):178-86.

Study Characteristics	Population	Intervention Groups	Results		Comments
			Measure	Outcome	
Lundstrom M 2007 **Sweden** **Setting** University hospital **Study Design** RCT **Randomization method** Sealed envelope. Stratified according to dislocation of fracture. **Study Length/Start-Stop Dates** 5/2000 – 12/2002 **Purpose** To determine whether a postoperative multi-factorial intervention program, including comprehensive geriatric assessment, management and rehabilitation, can reduce delirium and improve outcome in patients with femoral neck fractures. **Funding source(s):** Vardal Foundation, Joint Committee of the Northern Health Region of Sweden , JC Kempe Memorial Foundation, Foundation of the Medical Faculty, University of Umeå, County Council of Västerbotten and Swedish Research Council, Grant **Quality Score:** 6 **Risk of Bias**: High	**N = 353 patients assessed for eligibility** n = 154 excluded **N = 199 randomized and analyzed** **Inclusion** -Age ≥ 70 -Consecutively admitted to Orthopedic Department -Femoral neck fracture **Exclusion** N = 154 n = 95 did not meet inclusion criteria n= 11 Refused to participate n=27 missing due to failed inclusion routines n = 21 suffered fracture in hospital -severe rheumatoid arthritis -severe hip osteoarthritis -severe renal failure -pathological fracture -patients who were bedridden before fracture due to the operation methods that were planned to be used in the study Other assessments Geriatric Depression Scale (GDS) Prefracture Personal ADLs (P-ADL)	**n = 102 Intervention** n = 6 patients died during hospitalization n = 92 assessed at 4 months n = 86 assessed at 12 months Men and women (72.5%) Mean age 82.3 (6.6) **Protocol** -Patients randomized to the intervention group were admitted to a 24-bed geriatric unit specializing in geriatric orthopedic patients. -The staff applied comprehensive geriatric assessment, management and rehabilitation **Main content of intervention protocol** -Staff education -Teamwork -Individual care planning -Delirium prevention, detection, treatment -Prevention/treatment of complications -infection -anemia -embolism -Bowel/bladder function	**Delirium assessment:** MMSE Organic Brain Syndrome Scale (OBS) DSM – IV **Baseline characteristics** Depression Antidepressants **Primary outcomes** Days postoperative delirium Patients delirious postop Significant difference between groups for each day (1-7) Delirious after the seventh postoperative day Delirious at discharge **Secondary outcomes** Urinary infections Sleeping problems Falls Decubitus ulcers Assessments of underlying causes of delirium documented in medical records Length of Stay (LOS) (days) LOS for patients with postop delirium LOS for delirium patients with dementia Dementia patients with postop delirium at discharge	Delirium assessments by study nurses daily postop days 1-7; blinded specialist in geriatric medicine analyzed all assessments and documentation once during hospitalization No significant differences, except: **Intervention vs. Control** 32.4% vs. 47.4%, p 0.031 28.4% vs.46.4%, p 0.009 **Intervention vs. Control** 5.0 (7.1) vs. 10.2(13.3) p =0.009 54.9% vs. 75.3% p=0.003 p =0.001 18% vs. 52% p< 0.001 0 vs. 20 patients p < 0.001 **Intervention vs. Control** 39.3% vs. 60.3% p =0.018 28.6% vs. 50.7% p = 0.011 17.9% vs. 34.3% p = 0.034 10.7% vs. 23.6% p=0.059 2.28(1.25) vs. 0.90(0.90) p<.001 28(17.9) vs. 38(40.6) p= 0.028 31.4(19.3) vs. 43.6 (42.7) p= 0.032 3.2 (4.1) vs 12.8 (17.6), p = 0.003 0 vs 15, p <0.001	**Multivariate linear regression to control for baseline differences** **Dependent variable = number of days with postop delirium** **Independent variables (p)** -delirium post op (<0.001) -control group (0.001) -male sex (0.004) -depression (NS) -dementia (NS) -age (NS) Despite some baseline differences between the intervention and control groups, there was still a strong association between number of days with postoperative delirium and being treated in the control group. The effect of the intervention program seemed to reduce the incidence of delirium on the first postoperative day. This may be explained by the fact that, when the patients arrived at the intervention ward, they were immediately and systematically assessed to detect, treat and prevent any complications that would cause delirium. Patients with dementia seemed to have benefited from the intervention program. All parts of the intervention program, which are probably equally important should be systematically adapted with focus of detection, prevention and treatment of delirium Limitation -psychiatric symptoms and cognitive testing only 1 time during hospitalization
		n = 97 control Men and women (76.28%) Mean age 82 (5.6) **Protocol** Usual postoperative care in the orthopedic department Patients needing further in-hospital rehabilitation (n = 40) admitted to a geriatric ward but not the intervention ward	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Secondary outcomes** **Delirious control patients received** More sedatives More opioid drugs on demand	See above See above See above See above 41.7% *vs* 15.4%, p=0.008 61.7% *vs* 30.8%, *p*=0.004	

Conclusion: This study shows that postoperative delirium can be successfully treated by a team applying comprehensive geriatric assessment, management and rehabilitation. The intervention program resulted in fewer days with delirium, fewer other complications, and shorter hospital stays. Implementing this intervention program will probably have a great humanitarian and economic impact, and is probably applicable to surgery on old people in general. Therefore, the organization of surgical wards should be reconsidered and adapted to the needs of the oldest and frailest patients.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	Significant differences in baseline characteristics
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	No blinding during outcome assessment (record reviews)
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	1	Low	
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 6**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G3-G5-Milisen K, Foreman MD, Abraham IL, et al. A nurse-led interdisciplinary intervention program for delirium in elderly hip-fracture patients. J Am Geriatr Soc. 2001;49(5):523-32.

Study Characteristics	Population	Intervention Groups	Results		Comments
			Measure	**Outcome**	
Milisen K 2001 **Belgium** **Setting** Urban academic medical center **Study Design** Prospective longitudinal (pre/post design) **Selection method** Patients admitted to ER with traumatic fracture of proximal femur **Study Length/Start-Stop Dates** 9/1996 - 3/1997 9/1997 - 3/1998 **Purpose** To develop and test the effect of a nurse-led interdisciplinary intervention program for delirium on the incidence and course (severity and duration) of delirium, cognitive functioning, functional rehabilitation, mortality, and length of stay in older hip-fracture patients. **Funding source(s):** The Ministry of Public Health and Environment of the Belgian Government **Quality Score** 4 **Risk of Bias**: High	**N = 120 patients analyzed** n = 60 pre-intervention n = 60 post-intervention **Inclusion** -Patients admitted to the ER w/ traumatic fracture of proximal femur (intra-and extracapsular) -Hospitalized in one of two traumatological nursing units w/in 24 h of surgery -Spoke Dutch and verbally testable **Exclusion** -Multiple trauma concussion of the brain -Pathological fractures, surgery occurring more than 72 hours after admission, aphasia, -blindness -Deafness -Fewer than 9 years of formal education	**n = 60 intervention cohort** (9/1997 – 3/1998) Men and women (81.7%) Median age 82 (13) **Overview** -A system of enhanced quality of nursing care for older hip- fracture patients was developed, implemented, and tested. -Nurses identified high-risk patients and provided prompt anti-delirium interventions to reduce and treat delirium. -Access to readily available consultants and were able to administer regularly scheduled pain medications. Protocol components 1. Education of nursing staff 2. Systematic cognitive screening 3. Consultative services by -delirium resource nurse -geriatric nurse specialist -psycho-geriatrician 4. Use of a scheduled pain protocol	**Delirium assessment:** CAM MMSE **Baseline characteristics** Cardiac comorbidity Vascular comorbidity Abdominal comorbidity **Primary outcomes** Incidence of delirium, n% Duration of delirium (days) Severity of delirium *Mean total CAM scores* Intervention group range Control group range Linear mixed model analysis Cognitive function Sub-dimension memory Memory improvement over time Intervention effect on memory Overall cognitive functioning improved	Trained research nurses obtained information about cognitive functioning (CAM and MMSE) on the first, third, fifth, eighth, and twelfth postoperative days. Significant differences : **Intervention vs. Control** 13.3% vs. 30% p=.045 5% vs. 25% p=.004 5% vs. 20% p=.025 **Intervention vs. Control** 12 (20.0%) vs 14 (23.3%) (p = 0.82 – NS) 1 (1) vs. 4 (5.5), p=.03 **Delirium vs no delirium** 3.82 (2.8) to 1.91 (2.3) vs 0.98 (1.6) to0.87 (1.7) 6.92 (2.8) to 5.0 (3,.1) vs 1.35 (2,.3) to 0.76 (1.4) p = 0.0152, intervention vs control No significant difference in change over time Significant difference in decrease in CAM scores over time (less severity) in both cohorts (p = 0.0013) On average the CAM scores decreased by 0.082 units a day **Intervention vs control** p = 0.0357 (see figure 4) **Delirium vs no delirium** p = 0.0001 (both cohorts) p = 0.0087 both cohorts **Delirium vs no delirium** p = 0.0001 and p 0.0026	There was neither a statistical nor clinical effect for the intervention relative to functional status. There was no significant difference in functional status between the intervention and control cohorts or for either the delirious or nondelirious patients. However delirious patients in both cohorts were more dependent after discharge and 3 months after discharge. Neither cohort of the delirious patients regained their pre-fracture functional status. Delirious patients in both cohorts also had a slower functional rehabilitation over time. There was no significant difference in length of stay between intervention and control groups or between delirious and nondelirious patients Limitations -pre/post study design -less control of confounding variables -use of medical records to obtain historical data This study demonstrated the beneficial effects of an intervention program focusing on early recognition and treatment of delirium in older hip-fracture patients, with the delirious patients in the intervention cohort showing less severe delirium, shorter duration of delirium, and fewer memory problems.
		n = 60 pre-intervention cohort (control) (9/1996-3/1997) Men and women (80%) Median age 80 (12) **Protocol** Usual care	**Delirium assessment:** **Primary outcomes**	See above See above	

Conclusion: This study demonstrated the beneficial effects of an intervention program focusing on early recognition and treatment of delirium in older hip fracture patients and confirms the reversibility of the syndrome in view of the deliriums duration and severity.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	Significant differences in baseline characteristics
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	Pre/post design - no blinding
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	Pre/post design – no blinding
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Pre/post study with historical controls Baseline imbalances Possibility of confounding variables
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 4**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G3-G5-Rubin FH, Neal K, Fenlon K, et al. Sustainability and scalability of the hospital elder life program at a community hospital. J Am Geriatr Soc. 2011;59(2):359-65

Study Characteristics	Population	Study Process	Results		Comments
			Measure	Outcome	
Rubin 2011 **USA** **Setting** Community teaching hospital **Study Design** Quality improvement project **Selection method** Patients aged 70 and older on this unit who met the HELP criteria were enrolled **Study Length/Start-Stop Dates** 2001 – 2008 **Purpose** To describe the evolution of the HELP program at Shadyside over the 7- year period from 2002 to 2008, including the adaptations, patient outcomes, cost savings, challenges, and successes **Funding source(s):** Funded in part by Grants from the NIA, from the Retirement Research Foundation, from the Alzheimer's Association, and the Aging Brain Center, Institute for Aging Research, Hebrew Senior Life **Quality Score**: 3 **Risk of Bias**: NA – descriptive report	**Patients served (year)** N = 940 (2002) N = 4,044 (2005) N = 27,196 (2008) **HELP units** 2002 = 1 unit; 40 beds 2008 = 6 units, 184 beds **HELP staffing (FTEs)** 2002 = 1.8 FTEs 2005 = 5.5 FTEs 2008 = 7.5 FTEs **HELP volunteers** 2002 = 24 2005 = 52 2008 = 107 **HELP volunteer interventions (estimate)** 2002 = 5381 2005 = 24,000 2008 = 41, 880 **Inclusion** Age ≥ 70 Met HELP Criteria **Exclusion** Dx schizophrenia Using major tranquilizers/ antipsychotics Physical restraint during hospitalization	**Intervention** HELP initiated in 2002 Disseminated and expanded 2003 – 2008 -adoption of healthcare innovations -strong clinical leadership -support of senior management -credible supportive data -infrastructure supportive of innovation -organizational culture change -effective interdepartmental and interdisciplinary collaboration -responsive to immediate pressures and threats **Protocol** **Hospital Elder Life Program (from 2002 description)** Daily interventions targeted patients were not delirious and who were at intermediate risk for developing delirium Risk factors present: -cognitive impairment -sleep deprivation -immobility -visual or hearing impairment -dehydration Deviations from the original HELP model -exercise and fluid repletion protocols omitted due to insufficient staffing -sleep protocol modified -the Role of the nurse practitioner was modified to eliminate redundancies with existing services	Delirium assessment: CAM **Baseline data** Delirium rate **Primary outcomes** Delirium rate % (incident + prevalent) Reduction in delirium, percentage points Incident delirium 2004-2008 Patient satisfaction (range 1-3) Nurse satisfaction (range 1-3) Reduction from baseline in LOS Patients with delirium (days) Patients without delirium Cost saving, per year, $ **Challenges** Staff turnover Personnel conflicts Volunteer turnover Broad geographical coverage Paperwork reduction and tracking **Success** Met defined success metrics Prevention of delirium and shorter LOS Volunteer recognition	2002-2004 proxy assessment process validated by geriatricians and nurse practitioners. Beginning in 2004 direct bedside assessment using CAM **2001 (before HELP)** 41% Other baseline date not reported in this paper. **2002 / 2005 / 2008** 26% / 16% / 18% -15% / -25% / -23% ≤3% from 2004 to 2008 2.8 / 2.8 / 2.9 4.8 / 4.5 / NA 8.8(1.0) / NA / 7.0 (2.8) 6.0 (0.1) / NA / 5.3 (0.8) 1.23 million / NA / 7.37 million **Solutions/outcomes** Define roles, recruitment Team building efforts Enhance recruitment; academic credit for volunteers Develop satellite offices; stock offices with computers and supplies; Develop more efficient software and database system for volunteer assignments and data collection **Solutions and outcomes** Hospital-wide dissemination to 6 units Grand prize for hospital's Quality Improvement in 2003 and 2007 Volunteers receive widespread commendation, at hospital and local newspaper	The multiplicative expansion of the program during the 7 years reported attests to the scalability and generalizability of the HELP interventions. This program implementation demonstrated important positive outcomes in terms of -improving clinical care (reduction of delirium), -enhancing staff and patient satisfaction with care, -shortening hospital LOS - reducing costs of care, -fulfilling important clinical effectiveness and quality improvement goals -enhancing efficiency on a large scale within the hospital. The low rate of incident delirium (3%) among enrolled patients might represent a benchmark for delirium reduction programs. The low rates of observed delirium (≤3%) from 2004 to 2008, which are lower than observed rates in previous studies of HELP, may have been a reflection of the inclusion of lower-risk patients in that sample and the once-a-day clinical delirium assessments (as opposed to daily research assessments augmented by nursing interviews and medical record reviews in previous studies). The financial return of the program, estimated at more than $7.3 million per year during 2008, comprises cost savings from delirium prevention and revenue generated from freeing up hospital beds (shorter LOS of HELP patients with and without delirium).

Conclusion: The present study now makes the dissemination and financial case for HELP, which should clearly be a priority area for hospitals. In addition to preventing delirium, the program is effective for other important quality indicators, including falls, pressure ulcers, and LOS. The rising numbers of elderly inpatients compel all hospitals to carefully address their approaches to this population and to seriously consider HELP. This study can serve as a useful model for the successful implementation and dissemination of HELP.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	QI study
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	Unclear	QI study
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	Unclear	QI study
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Historical controls
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 4**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G5-Cole MG, Primeau FJ, Bailey RF, et al. Systematic intervention for elderly inpatients with delirium: a randomized trial. CMAJ. 1994;151(7):965-70.

Study Characteristics	Population	Intervention Groups	Results		Comments
			Measure	**Outcome**	
Cole MG 1994 **Canada** **Setting** University-affiliated Hospital **Study Design** RCT **Randomization method** Randomly allocated to treatment or control group by blinded RA **Study Length/Start-Stop Dates** 8 weeks **Purpose** To determine whether systematic detection and treatment of elderly medical inpatients with delirium would reduce cognitive impairment, abnormal behavior, functional disability, use of restraints, length of hospital stay, need for increased care after discharge and rate of death. **Funding source(s):** St Mary's Hospital Foundation **Quality Score** 3 **Risk of Bias**: High	**N = 174 SPMSQ ≥5** N = 88 dx with delirium **Inclusion** Age ≥75 Admitted to medical department English or French language Score ≥5 on SPMSQ **Exclusion** N = 488 n = 47 ICU admission n = 84 cardiac monitoring unit (CMU) admission n = 49 oncology admission n = 196 geriatric services admission n = 47 language barrier n = 22 discharge n = 8 death n = 33 combination of reasons n = 2 refusal **Assessment tools**: Confusion Assessment Method (CAM) Short Portable Mental Status Questionnaire (SPMSQ) Crichton Geriatric Behavioral Rating Scale (CGBRS) **Follow up by RA (data collection**) 1. Presence of initial consultation in patient record 2. Use of restraints 3. Length of stay during the study period 4. Discharge information (location..home..facility) Compliance with initial recommendations Dates of follow up, new recommendations, compliance	**n = 42 treatment group** n = 3 discharged or died before RA first assessment **n = 39 analyzed** Men and women (71.4%) Mean age 86.8 (5.9) Consultation by a geriatrician or geriatric psychiatrist -within 24 h after referral -chart review -interview with patient or family -interview with clinical staff -determine previous med and psych hx -confirmed delirium dx -determined probable cause(s) -made treatment recommendations -recorded findings and recommendations on the regular hospital consultation form in patient chart Follow up by a liaison nurse (see "Nursing Intervention Protocol" Table 1 in PDF) -daily follow up for up to 8 weeks -confirm recommendations implemented -consulted with patient's nurse(s) -checked with consultant if patient management problems -conducted weekly patient mental status assessment Delirium reassessment by RA on weeks 1, 2, 4, and 8 Follow up by RA as listed	**Delirium assessment:** CAM DSM III SPMSQ CGBRS **Baseline characteristics** Gender (more women) **Outcomes** Delirium alone Dementia + delirium Other psych dx + delirium Initial recommendations Compliance Mortality SPMSQ and CGBRS SPMSQ CGBRS	Initial CAM assessment by study nurse for delirium dx per DSM III; enrollment and randomization if positive for delirium. After random allocation, a blinded RA completed the 1st assessment using SPMSQ and CGBRS; RA reassessed for delirium on weeks 1, 2, 4, and 8 **Significant differences** Treatment vs control 71.4% vs 58.7% *Treatment group* 11 (285%) 22 (56%) 6 (16%) 39 (100%) (investigations; drug prescriptions; other; combination) Range = 77% to 97% Treatment vs control 33% vs 37% **N = 57 (all patients)** **Treatment + control** Initial scores were higher (patients more impaired) among those who died that those who survived but NS Improved over time (<0.05) Improved marginally (<0.06) Pattern of improvement did not change when those who died were added to the analysis	**Disposition of 88 patients at 8 weeks** - 44 discharged from hospital - 13 remained hospitalized - 31 died (35%) **No significant difference between groups** -use of restraints -LOS -discharge rate -discharge to a setting providing higher level of care than before admission -mortality rate **Patients in the treatment group** without dementia (p <0.05) or with a specific cause of delirium (p <0.02) were more likely to improve at 2 weeks. While the improvement in CBGRS scores in the treatment group compared to the control group was not statistically significant, it probably is clinically relevant. Excluding patients admitted to the geriatric department may have had more treatable condition Patients who developed delirium during their hospital stay (incident) rather than those who were delirious at admission (prevalent) may have been more treatable. The characteristics of the enrolled patients (very old, very ill, high mortality and more than half with dementia and delirium) may have reduced the effect of the intervention.
		n = 46 control group n = 14 had a geriatrician/psychiatrist consultation during the study period Men and women (58.7%) Mean age 85.4 (6.3) Usual medical care RA also collected -baseline assessment data -use of restraints -length of stay during study period -whether delirium had been detected by the attending physician Attending/clinical staff could request a geriatrician or geriatric psychiatrist consultation	**Delirium assessment:** **Baseline characteristics** **Outcomes** Delirium dx by attending	See above RA 1st assessment and at 1, 2, 4, and 8 weeks No significant differences between patients who were and were not referred for a geriatrician/ psychiatrist consultation while receiving usual care (control) 16%	
Conclusion: The beneficial effect of a systematic detection and intervention in cases of delirium in elderly patients was small in this study. This could be addressed in future studies bty targeting cases more likely to respond or by intervening more intensively,					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	Unclear	More women in treatment group
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	1	Low	
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	High	35% deaths
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	0	Unclear	Some outcomes = 57 (treatment + control); some = 88 all enrolled
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	No ITT
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	0		<50 each group
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 3**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

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  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G5-Cole MG, McCusker J, Bellavance F, et al. Systematic detection and multidisciplinary care of delirium in older medical inpatients: a randomized trial. CMAJ. 2002;167(7):753-9.

Study Characteristics	Population	Intervention Groups	Results		Comments
			Measure	Outcome	
Cole MG 2002 **Canada** **Setting** 5 medical units – University Hospital **Study Design** randomized trial **Randomization method** Computer generated random numbers (stratified within groups of prevalent and incident and blocks of different sizes to preserve blinding **Study Length/Start-Stop Dates** 3/1996 to 1/1999 **Purpose** To determine whether systematic detection and multidisciplinary care of delirium in older patients admitted to a general medical unit could reduce delirium in older patients and could reduce time to improvement in cognitive status. Secondarily to reduce symptoms of delirium, increase independence and rate of discharge to the community. Also to improve survival during 8 weeks after enrollment , decrease hospital lengths of stay and improve outcomes for incident and prevalent delilrium with and without dementia. **Funding source(s):** Grant - National Health Research Development Program of Health Canada. **Quality Score** 6 **Risk of Bias**: High	**N = 5216 age ≥65 admitted to medical units** n = 3291 excluded (see below) n = 1925 eligible for screening **N = 299 prevalent or incident delirium** n = 72 did not consent **N = 227 randomized** N = 113 intervention N = 114 usual care **Inclusion** Age ≥65 Prevalent delirium at admission Incident delirium within 1 week Informed consent by patient or decision maker **Exclusion** N = 3291 n = 362 stroke n = 326 language barrier n = 117 not Montreal resident n = 209 >48 h in ICU n =310 in CMU n = 640 oncology admission n = 337 geriatrics admission n = 460 long term care unit n =82 discharged n = 29 died n = 116 previously enrolled n = 92 communication problem n = 155 refused screening n = 56 other reason **All patients assessment** Blinded RA within 24H: Baseline MMSE Delirium Index Barthel Index Collected demographic and clinical (chart) information Family interview: Informant Questionnaire on Cognitive Decline in the Elderly **Follow up** RA yusing process of care checklist Chart review by nurse abstractor (Charlson comorbidity index	**n = 113 Intervention group** n = 110 received intervention n = 7 withdrawn n = 106 completed trial Men and women (58.4%) Mean age 82.7 (7.5) Study nurse not blinded to intervention 1. Consultation and follow up by geriatric internist or psychiatrist -determine predisposing, precipitating and perpetuating factors of delirium -made management recommendations 2. Follow up by study nurse -daily visit (mean 35.7 min) -assure implementation of recommendations -assure nursing protocol implementation (see Table 1 in PDF) -meet with/involve patient family	**Delirium assessment:** CAM SPMSQ (dx DSM III R) **Baseline characteristics** **Primary outcomes** Prevalent delirium NS risk if prevalent Incident delirium Delirium + dementia NS for delirium + no dementia Improvement in MMSE score Severity of illness score Charlson comorbidity index NS for less comorbidity Time to improvement Delirium Index Score	Screened at admission by SPMSQ and CAM by nurses for prevalent delirium and 1 week later for incident delirium before randomization; CAME and MMSE inter-rater reliability “excellent” No significant difference between groups **Intervention vs usual care** No significant difference between groups for any outcome 80.5% vs 80.7% 1.15 (0.48-2.79) 19.5% vs 19.3% 59.3% vs 56.1% HR 1.54 (0.82-2.97) 48% vs 45% 5.8 (1.2) vs 5.8 (1.3) 3.2 (2.2) vs 3.3 (2.1) HR 1.36 (0.75-2.46) NS trend toward shorter time for intervention group 48% vs 45% HR 1.10 (0.74-1.63) 8.34 (3.87) vs 7.36 (3.49) HR 1.09 (0.74-1.60) The results of the efficacy analysis did not differ from the main analysis	**Changes from prior study:** -more intensive -consultant followed patients -study nurse visited 5 x week -study team (2 geriatric internists, 2 geriatric psychiatrists, study nurse) met to discuss delirium management problems -primary investigator met weekly with study nurse to discuss dx, enrollment, interventions. There were no deviations from the planned study protocol Delirium may be an epiphenomenon related to the severity of medical illness; consequently the psychosocial component of the intervention may have been superfluous In the absence of an effective intervention strategy for prevalent or incident delirium in older patients, research efforts should focus on prevention of delirium in this population. This might involve identification of potentially modifiable predisposing or precipitating risk factors for prevalent delirium and evaluation of interventions aimed at risk factor abatement.
		n = 114 Usual care group n = 114 received yusual care n = 2 withdrawn n = 112 completed trial Men and women (50%) Mean age 82.0 (7.1) Usual care -standard hospital services -consultation requests honored -no systematic follow up by geriatric specialists or nurse if consultation provided -dx of delirium not provided to hospital staff	**Delirium assessment:** **Baseline characteristics** **Primary outcomes**	See above See above See above	

Conclusion: Systematic detection and multidisciplinary care of delirium does not appear to be more beneficial than usual care for older patients admitted to medical services.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	Study nurse not blinded
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	Study nurse not blinded
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	1	Low	
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 6**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G5-Mador JE, Giles L, Whitehead C, Crotty M**.** A randomized controlled trial of a behavior advisory service for hospitalized older patients with confusion. Int J Geriatr Psychiatry. 2004;19(9):858-63.

Study Characteristics	Population	Intervention Groups	Results		Comments
			Measure	**Outcome**	
Mador JE 2004 **Australia** **Setting** 2 Metropolitan Teaching Hospitals **Study Design** RCT **Randomization method** Pharmacy department in one of the study hospitals (by person external to the study) in blocks of 10 stratified for the 2 hospitals (computer generated table of random numbers) **Study Length/Start-Stop Dates** 10/2002-8/2003 **Purpose** To determine whether individualized advice on non-pharmacological strategies for hospitalized older patients with confusion and behavioral problems can improve levels of agitation and reduce the use of psychotropic medication. **Funding source(s):** Medical Benefits Fund of Australia Health Research Award and the Department of Veteran Affairs, Australia **Quality Score** 4 **Risk of Bias**: High	**N = 127 assessed for eligibility** n = 56 excluded (see below) **N = 71 randomized** **Inclusion** Age ≥60 Medical or surgical inpatient Confused due to -dementia (DSM-IV) -delirium (CAM) -combination Behavioral disturbance that was problematic to ward staff Informed consent by family member **Exclusion** N = 56 n = 16 presence of primary psychiatric illness (responsible for behavioral disturbance) n = 5 absence of next of kin to consent n = 17 no behavioral problem n = 5 confusion resolved n = 7 age <60 n = 3 next of kin refused n = 3 missed (not randomized) **Trial period** Time of randomization until the time of discharge or the date on which the patient was approved for discharge to a residential care facility **Assessment tools** Pittsburgh Agitation Scale (PAS) Medication Appropriateness Index (MAI) Total daily doses of benzodiazepines and antipsychotics	**n = 36 intervention** n = 2 deceased n = 34 discharged Men and women (42%) Mean age 82.1 (80.0 – 84.3) Prior residence = home 64% Current geriatrician = 61% Delirium only 6% Dementia only 50% Delirium + dementia 44% Patients referred to the Extended Practice Nurse (EPN) in aged care - Seen by the EPN within 24h of randomization -assessed patient -formulated management plan (non-pharm) -discussed plan with ward nurses -provided ongoing support and education to nursing staff Non-pharm plan -tailored to patient needs -addressed safety issues -close supervision -minimized restraint use -reduced falls risk -communication with patient -basic nursing care -targeted behavioral strategies -education for nursing staff (reframing behavior and triggers)	**Delirium assessment:** CAM at admission **Baseline characteristics** Prior residence = home Current geriatric care **Primary outcomes** PAS PAS subgroup analysis Initial PAS ≥4 Sleep Restraint use MAI Doses of antipsychotics Doses of benzodiazepines **Secondary outcomes** Length of stay Faller status Nursing satisfaction Next of kin satisfaction Discharged to residential care (if admitted from home)	Ongoing assessment not described **Significant difference between groups** **Intervention (36) vs control (35)** 64% vs 86%, p = 0.035 61% vs 29%, p = 0.006 No other significant differences between groups at baseline **Intervention (36) vs control (35)** 1.7 (0.4) vs 1,.8 (0.3) NS (p = 0.369) n = 12 vs 17 NS (p = 0.713) NS (p = 0.212) NS OR 0.42(0.07-2.51), p = 0.345 NS (p = 0.061) NS (p = 0.817) NS (0.730) NS (p = 0.557) NS (p = 0.083) NS (p = 0.497) NS (p=0.488) NS (0.577)	No patients were lost to follow up Data on deceased patients included in analysis (ITT) Possible reasons the intervention was ineffective -EPN advice may not offer an advantage over medical advice from a geriatrician or care nursing staff are already providing -adherence to EPN advice not measured -may have been more effectively delivered by a multidisciplinary team -patients cared for on same ward so nurses may have delivered useful strategies to control group -patients may not have been agitated enough at baseline to show significant improvement -study may have been under powered
		n = 35 control n = 2 deceased n = 33 discharged Men and women (54%) Mean age 82.9 (81,4-84.5) Prior residence = home 86% Current geriatrician = 29% Delirium only 9% Dementia only 54% Delirium + dementia 37% Usual care by a geriatrician for medical advice of the patient's confusion and behavioral disturbance	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Secondary outcomes**	See above See above See above See above	

Conclusion: A nursing consultation service providing individualized non-pharmacological advice does not improve patient agitation or use of psychotropic medication for older patients with confusion and behavioral problems in an acute hospital.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	Significant differences between groups
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	Unclear	Blinding for some outcomes but clinicians not blinded
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Significant baseline imbalances (ITT analysis done)
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		? only for initial assessment
8. **Sample size ≥50 each study arm (1 point if achieved)**:	0		<50 each group
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 4**

Instructions on rating:

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  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G5-Marcantonio ER, Bergmann MA, Kiely DK, Orav EJ, Jones RN. Randomized trial of a delirium abatement program for postacute skilled nursing facilities. J Am Geriatr Soc. 2010;58(6):1019-26.

Study Characteristics	Population	Intervention Groups	Results		Other functions associated with the study
			Measure	Outcome	
MarcantonioER 2010; USA **Setting** Multicenter (8) Skilled nursing facilities **Study Design** Cluster RCT **Randomization method** After matching on ownership status, size, and setting (urban vs suburban) facilities randomized to DAP or usual care (patient randomization based on facility) **Study Length/Start-Stop Dates** 10/2000-12/2003 **Purpose** To determine whether a delirium abatement program (DAP) can shorten duration of delirium in new admissions to postacute care (PAC) **Funding source(s):** National Institute on Aging Grant and Paul Beeson Physician Faculty Scholar in Aging Research **Quality Score** 4 **Risk of Bias**: Unclear	**N = 457 enrolled (consent)** n = 282 DAP n = 175 usual care **NOTE:** See detailed CONSORT flow chart (PDF p 1022) for facility inclusions/ exclusions and patient inclusions/exclusions **Inclusion (facilities)** Boston-area skilled nursing facilities ≥ 35 PAC admissions/ month Facility leadership supported study participation Minimum threshold for quality of care based on state survey results **Inclusion (patients)** Age ≥65 Admitted directly from an acute medical or surgical hospitalization English speaking Able to communicate before acute illness Life expectancy >6 mo Lived within 2,5 miles of research site **Exclusion** N = See detail in CONSORT chart (p 1022 in PDF) End stage dementia Complete functional dependence before hospitalization Refused (patient or caregiver) **Eligibility** Study personnel screened all new PAC admissions for trial eligibility (delirium assessment) Proxy interviews to obtain information associated with -Charlson scale -pre-hospitalization self care function (for ADLs) -DSM IV criteria for dementia -reviewed medical records for dx codes	**n = 282 Delirium Abatement Program** Men and women (61%) Mean age 83.8 (7.4)) **Nursing implementation of DAP** -Long-term Care Resident Assessment Instrument (v2) -nurses blinded to results of RA eligibility assessments -all nurses educated (CME based pre and post testing) -DAP facilities received the eligibility assessment materials (not results) -environmental modifications provided -5 measures of DAP implementation developed and monitored quarterly -tip sheets provided to assist with implementation -Delirium Resource Nurse identified and given extra training -Assessment of Causes form -delirium nursing care plan -at least 2 environmental modifications placed in each patient's room -DAP facilities received small incentive payments based on performance (up to $700 every 6 months)	**Delirium assessment:** CAM MMSE DSI Digit Span **Baseline characteristics** White race Clinical dementia **Primary outcomes** DAP structured delirium assessment Delirium triggered in med record Assessment of causes completed Nursing care plan completed Environmental modifications performed Detection of delirium Persistence of delirium Rates of death	Eligibility assessment: Trained researches completed a structured interview within 5 days of admission using CAM, MMSE, Digit Span and DSI Ongoing assessments by trained RAs (blinded) using the CAM algorithm Significant difference between groups **DAP vs usual care** 96% vs 84%, p <.01 46% vs 32%, p <.01 DAP adherence (n = 282) 75% 41% 38% 33% 35% **DAP vs usual care** 41% vs 12 %, p <.001 The majority of cases remained undetected at all facilities There was little evidence to suggest that more interventions were performed at DAP than at usual care sites No difference between groups At 2 weeks (67.8% vs 65.7%, p = .77) At 1 month (59.9% vs 509.7%, p = .48) No difference between groups At 2 weeks (2.1% vs 2.3%, p = .89) At 1 month (8.5% vs 9.1%, p = .78)	**Administrative Advisory Council (AAP)** (Facilities) -administrative leaders -nursing leaders -medical leaders Met every 3 months at DAP sites; every 6 months at usual care sites **AAP Role** Reviewed processes -patient screening -consent -follow up -adherence at DAP sites **DAP sites** -introductory letter to physicians and nurse practitioners -semiannual newsletter to update personnel -highlighted important aspects of delirium detection and management **Delirium Management** Trained nurse conducted identical reviews of DAP and usual care sites' medical records to identify important processes: -documentation, by physicians/nurse practitioners -evaluation and treatment for reversible causes -prevention and management of common complications -restoration of function
		n = 172 usual care Men and women (69%) Mean age 84.4 (7.2)) Usual care	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Secondary outcomes**	See above See above See above See above	

Conclusion: Detection of delirium improved at the DAP sites, but the DAP had no effect on the persistence of delirium. This effectiveness trial demonstrated that a nurse-led DAP intervention was not effective in typical PAC facilities.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	Patient significant differences at baseline
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	Unclear	No detail provided on how randomization was performed
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	Unclear	DAP facilities aware of intervention status
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	Unclear	Multivariate analysis using baseline imbalances did not change outcome data All patients included in outcomes but not specific ITT design
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = Unclear**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 4**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G5-Pitkala KH, Laurila JV, Strandberg TE, Tilvis RS**.** Multicomponent geriatric intervention for elderly inpatients with delirium: a randomized, controlled trial. J Gerontol A Biol Sci Med Sci. 2006;61(2):176-81.

Study Characteristics	Population	Intervention Groups	Results		Comments
			Measure	Outcome	
Pitkala KH 2006 **Finland** **Setting** General medicine units (6) City Hospital **Study Design** RCT **Randomization method** Computer generated random numbers assigned consecutively by blinded staff member **Study Length/Start-Stop Dates** 9/2001-11/2002 **Purpose** To investigate whether a comprehensive geriatric assessment and individually tailored treatment are effective in reducing mortality and permanent institutional care among patients with delirium. Also to determine whether this treatment is beneficial in reducing the number of days spent in institutions, alleviating delirium, or improving cognition or physical functioning of these patients. **Funding source(s):** Lions Organization, Helsinki University Central Hospital, Academy of Finland **Quality Score**: 7 **Risk of Bias**: Unclear	**N = 2040 admitted (>69 yr)** n = 350 not eligible for screening N = 1690 screened N = 379 CAM positive n = 205 excluded **N = 174 met DSM IV criteria** n = 87 intervention n = 87 control **Inclusion** Age >69 Informed consent from closest proxy **Exclusion** N = (see below) *Not screened (305)* n = 118 admission from permanent institutional care facility n = 202 discharged <48 h n = 30 refused screening *Screened/excluded* n = 23 refused n = 24 terminal prognosis n = 4 discharged before delirium dx confirmed n = 10 permanent institutional care n = 15 no caregiver/consent n = 129 did not meet DSM IV criteria **All patients protocol** Screened within 2 days of admission (baseline) -CAM, MMSE, Digit Span -proxy interview -premorbid dementia status (CDRS; DSM IV) -med record review -comorbidities (CMI) Follow up at 3&7 6 months -MMSE -Barthel Index -IADL scale -Geriatric Depression Scale -Mini-Nutritional Assessment -proxy interview	**n = 87 intervention** n = 87 follow up 3 & 6 months Men and women (75.9%) Mean age 83.8 (5.6) 1. Accurate dx of delirium 2. Comprehensive geriatric assessment 3. Avoid conventional neuroleptics in favor of atypical antipsychotics 4. Orientation 5. Physiotherapy 6. General geriatric interventions -nutritional supplements -calcium + vitamin D -hip protectors 7. Cholinesterase inhibitors if MMSE <23 -also MRI or CT if cognition impaired after delirium resolution 8. Comprehensive discharge planning -consultation with social worker -occupational therapist home visit -discharge planning with caregiver(s)	**Delirium assessment:** CAM MMSE Digit Span DSM IV Memorial Delirium Assessment Scale (MDAS) **Baseline characteristics** **Primary outcomes** Atypical antipsychotics Conventional neuroleptics Acetylcholinesterase inhibitors Vitamin D + calcium Nutritional supplements Hip protectors Physical therapy Specialist consultations CT or MRI scans Intensity and severity of delirium symptoms improved at 6 months (MMSE score) Delirium days (mean, SD) Deceased Admitted to permanent institutional care	Admission screen by 2 trained study nurses following standardized procedures using CAM and MMSE; positive CAM assessed by study physician; delirium dx confirmed by DSM IV criteria. Daily MDAS during first week in hospital and every second day thereafter No significant differences between groups **Significant difference in treatment interventions % vs %, p** **Intervention (87) vs Control (87)** 69.0% vs 29.9%. p <.001 8.0% vs 23,.0%, p = .006 58.5% vs 9.3%, p <.001 77.0% vs 9.3%, p <.001 92.0% vs 0.0%, p <.001 90.8% vs 1.1%, p <.001 89.7% vs 44.8%, p <.001 49.4% vs 28.7%, p = .005 51.7% vs 8.0%, p <.001 18.4 vs 15.8, p = 0.047 **No significant difference between groups** 29.3 (25.6) vs 22.4 (18,.4), p = .171 34.5% vs 29.9%, p = .516 42.5% vs 51.7%, p = .224	Systematic methods on screening or preventing delirium are not used in the study hospital This intervention did not improve patients' general prognosis as indicated by no effect on mortality, institutionalization or length of hospital stay with delirium In the case of full blown delirium, this type of intervention may be "too little too late" to produce a significant difference in prognosis and thus, even more effort should be focused on prevention of delirium among such patients. Post hoc analysis of patient and intervention factors impacting prognosis: -Barthel Index score significant for mortality HR 2.1 (1.1-4.0) -nutritional supplements protected against death HR 0.3 (0.1-0.8) Antipsychotics and ChEIs did not affect mortality
		n = 87 control n = 83 follow up 3 & 6 months n = 4 refused assessments but allowed medical record retrieval of endpoint data Men and women (71.3%) Mean age 83.3 (6.2) Usual care	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Secondary outcomes**		

Conclusion: This study is the third randomized trial showing no effect of geriatric intervention on the prognosis for delirium. Good, comprehensive geriatric treatment is justified in this patient group because of more effective alleviation of delirium and improved cognition. However, individual cases deserve careful tailoring of treatment and evaluation whether they benefit from active, curative treatment or good palliative care.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	No comment on blinded outcome assessment
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	1	Low	
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = Unclear**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 7**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G5-Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet. 2009;373(9678):1874-82.

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects Comments
			Measure	Outcome	
Schweickert WD 2009 USA **Setting** Multicenter (2) University hospitals **Study Design** RCT **Randomization method** 1:1 allocation by computer generated permuted blocks by consecutively numbered sealed envelopes by investigator with no further involvement in the study; assessment therapists were different than intervention therapists **Study Length/Start-Stop Dates** Not described **Purpose** To assess the efficacy of combining daily interruption of sedation with physical and occupational therapy on functional and neuropsychiatric (such as ICU-associated delirium) outcomes in patients receiving mechanical ventilation in intensive care. **Funding source(s):** Identified as "none" No conflicts of interest listed by authors **Quality Score:** 6 **Risk of Bias:** Unclear	**N = 1163 patients screened** n = 343 excluded N = 818 eligible for enrollment n = 714 excluded **N = 104 randomized** n = 49 intervention n = 55 control **Inclusion** Age ≥18 On mechanical ventilation <72 h Mechanical ventilation expected to continue >24 h Baseline functional independence (Barthel score ≥70 – obtained from proxy re patient function 2 weeks before admission) **Exclusion** N = see below *Excluded at screening* N = 343 n = 1 aged < 18 n 161 mechanical ventilation >72h n = 181 dependent prior functional status *Excluded from enrollment* n = 150 no consent n = 173 extubation order n = 122 cardiac arrest n = 126 irreversible condition (>50% 6 month mortality) n = 103 rapidly developing neurologic/neuromuscular disease n = 30 conflicting study n = 5 advanced dementia n = 1 raised intracranial pressure n = 6 multiple absent limbs Enrollment in another trial **All patients** Goal directed sedation guided by Richmond Agitation Sedation Scale (RASS) Protocol for weaning from mechanical ventilation	**n = 49 intervention** No patients discontinued protocol or lost to follow up Men and women (59%%) Mean age (range) 57.7 (36.3-69.1) Exercise and mobilization (physical and occupational therapy) Daily protocol -sedatives interrupted -unresponsive patients underwent passive range of motion exercise in all limbs -if patient able to interact, active assisted and/or active independent range of motion exercises in the supine position -as tolerated, treatment was advanced and bed mobility activities initiated -sitting balance activities followed by ADLs and exercised that increased functional independence -progressed to transfer training and pre-gait exercises -therapy continued daily until patient reached previous level of function or discharge	**Delirium assessment:** CAM-ICU RASS **Baseline characteristics** **Primary outcomes** Mean duration of PT, OT (hr/day) Time from intubation to first PT/OT session (d) Return to functional status Time to functional milestones ICU delirium (d) Time in ICU with delirium (%) Hospital days with delirium (d) Age Absence if sepsis PT/OT intervention	Daily independent neurological assessments by non-blinded study personnel using the RASS for level of arousal and CAM-ICU for delirium and coma (inter-rater reliability and severity not discussed) No significant difference between groups **Significant differences between groups Intervention (49) vs Control (55)** 0.32 (0.17-0.48) vs 0.0; p <0.0001 1.5 (1.0-2,.1) vs 7.4 (6.0-10.9); p <0.0001 59% vs 35%; p = 0.02 OR 2.7(1.2-6.1) P <0.001 for all (Table 4) 2.0 (0.0-6.0) vs 4.0 (2.0-7.0) p = 0.03 33% (0-58%) vs 57% (33-69%), p = 0.02 2.0 (0.0 -6.0) vs 4.0 (2.0-8.0), p = 0.02 **Variables associated with achievement of functional independence HR (CI), p** 0.96 (.94-.98), p = 0.001 2.26 (1.03-4.97), p = 0.04 1.84 (1.02-3.31), p = 0.04 **No significant difference between groups** -sedation and analgesia practice -occurrence and duration of daily interruption of sedation -proportion of time on mechanical ventilation spent receiving sedative or opiate -high spontaneous breathing trial performance rates -reasons and occurrence rates for unsuccessful spontaneous breathing trials -ICU length of stay	Deaths before discharge (NS) Intervention N = 9 (18%) Control N = 14 (25%) Deaths before intervention N = 3 Discontinuation of therapy due to patient instability in 4% of all sessions (most commonly for perceived patient-ventilator asynchrony) **Comments** Patients in the intervention group had a shorter duration of ICU-associated delirium by 2.0 days and spent 2-4 more days alive and breathing without assistance than controls. Early physical and occupational therapy, combined with daily interruption, was safe and well tolerated. Delirium and neuromuscular function are undoubtedly linked. Without intact cognition, physical activity is either self-limited or iatrogenically limited, cooperation with therapy is poor and any immobilization injury is likely exacerbated.
		n = 55 control No patients discontinued protocol or lost to follow up Men and women (42%) Mean age (range) 54.4 (46.5-66.4) Usual care (PT or OT only as ordered by primary care team)	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Secondary outcomes**	See above See above See above See above	

Conclusion: A strategy for whole-body rehabilitation accomplished by interruption of sedation, protocol-driven spontaneous breathing trials, and physical and occupational therapy resulted in better outcomes compared with current standard approaches to sedation and activity during mechanical ventilation and its recovery,. Patients assigned to intervention had shorter duration of delirium and left the hospital with better functional status. Robust outcomes can be achieved with the coordinated efforts of multiple disciplines dedicated to the survival and mental and physical recovery of critically ill patients receiving mechanical ventilation.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	Unclear	Delirium assessors not blinded
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	1	Low	
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = Unclear**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	0		<50 intervention group
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 6**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G1 G2- Mouzopoulos G, Vasiliadis G, Lasanianos N, et. el., Fascia iliaca block prophylaxis for hip fracture patients at risk for delirium: a randomized placebo-controlled study, J Orthop Traumatol. 2009; 10(3):127-33.

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects/Comments
			Measure	**Outcome**	
Mouzopoulos G 2009 **Greece** **Setting** Inpatients in orthopedic ward **Study Design** RCT -placebo-controlled, **Randomization method** Orthopedic surgeons, neurologists and nurses identified potentially eligible patients by systematically screening new admissions to one orthopedic ward; patients with intermediate or high risk of delirium were sequentially randomized to treatment or placebo using a computer generated code; all participants blinded to study group allocation **Study Length/Start-Stop Dates** 07/2004-03/2008 **Purpose** To assess the effectiveness of fascia iliaca compartment block (FICB) for prevention of perioperative delirium in hip surgery patients who were at intermediate or high risk for this complication. **Funding source(s):** Not disclosed **Quality Score** 4 **Risk of Bias**: High	**N = 324 admitted to orthopedic department** N = 37 excluded before screening N = 287 screened n = 53 low delirium risk **N = 219 randomized** **n = 108 FICB** **n = 111 placebo** **Inclusion** Age ≥70 years Admitted for hip fractures **Exclusion** **N= 37 (not screened)** 13 Refused to participate 11 taking antipsychotic drugs 4 = Parkinsonism 4 = pathologic hip fracture (metastasis) 2 = acute MI at admission 2 = delirium at admission **Baseline exclusions** 13 = refused study drug tx 2 = died before study started 53 = low risk **Screening Risk Factors** Severity of illness -acute physiology -age -chronic health exam Cognitive impairment (MMSE) Index of dehydration Visual impairment **Definition of Risk** Intermediate risk = 1 or 2 risk factors present High risk = 3 or more risk factors present	**n = 108 FICB group** **Dropouts** n=1 died n=3 denied participation n=2 lost at follow-up **n = 102 analyzed** Intermediate Risk = 85 High Risk =17 Age (years) = 72.3 ± 4.1 Men and Women (23.5%) APACHE II score = 12.89 ± 2.13 MMSE score = 24.1 ± 3.6 Visual acuity = 0.4 ± 0.12 Dehydration index = 20.15 ± 3.47 *Intervention* 0.25 mg bupivacaine on admission and every 24 h until delirium occurrence or surgery. 24 h post-op FICB was re-administered and repeated daily every 24 h until delirium or discharge. A standardized FICB technique was used for the patients. Pain was treated with paracetamol (1 g/6.7 ml) and pethidine (50 mg) as needed	**Delirium assessment:** CAM DRS-R-98 Digit span - attention DSM-IV **Baseline characteristics** Patients who developed delirium **Primary outcomes** Incidence of delirium *All patients* Relative risk OR (CI) *High risk patients* Relative risk OR (CI) *Intermediate risk patients* Relative risk OR (CI) **Secondary outcomes** *Severity of delirium* DRS-R-98 highest value Mean difference (CI) *Delirium duration (days (CI))*	Daily assessments by experienced nurses and geriatricians based on a structured multimodal protocol including delirium assessment and severity if diagnosed; specific training and inter-rater reliability not discussed No significant difference between groups No significant difference between groups **FICB v placebo group** **N = 102 vs 105** 11(10.8%) v 25 (23.8%) 0.45 (0.23 to 0.87) 9/17 v 10/16 0.84 (0.47 to 1.52) 2/85 v 15/89 0.13 (0.03 to 0.53) 14.34±3.6 v 18.61±3.4, 4.27 (1.8 to 5.64) p <0.001 5.22 ± 4.28 v 10.97 ± 7.16 (3.87 to 7.62) p <0.001	There were no complications of FICB administration, except three local hematomas developed at the injection site, which resolved spontaneously. **Comments** No significant difference between groups in use of pain medication and no correlation with development of delirium No significant difference between groups for delirium for patients classified as high risk, but there was a significant risk reduction for FICB patients classified as intermediate risk (p not provided) Although the study controlled for perioperative risk factors it did not examine the impact of drugs other than paracetamol and pethidine,
		n = 111 placebo group n= 2 died n= 4 lost to follow-up **n = 105 analyzed** Intermediate Risk = 89 High risk = 16 Age (years) = 73.1 ± 3.8 Men and Women (22.4%) APACHE II score = 12.97 ± 1.82 MMSE score = 24.43 ± 3.2 Visual acuity = 0.42 ± 0.08 Dehydration index = 20.24 ± 3.15 *Intervention* Placebo medication (water for injection) was identical in appearance to the active drug and was administered identically as the FICB was injected. Intramuscular analgesics were administered as needed in both groups. paracetamol (1 g/6.7 ml) and pethidine (50 mg) for pain as needed	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Secondary outcomes**	See above See above See above See above	

Conclusions: Delirium incidence was reduced after FICB injection in patients who had sustained hip fracture, especially those who were at intermediate risk for this complication. FICB, either in its own right or versus opioid regimens, leads to better delirium outcomes.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	Unclear	Not clear if outcome assessors were blinded; only patients
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	High	Dropouts after randomization not included in analysis
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	0	Unclear	Incidence p values not included and dropouts were excluded from analysis
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	No ITT analysis Funding not disclosed
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 4**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G2-Kinjo S, Lim E, Sands LP, et al. Does using a femoral nerve block for total knee replacement decrease postoperative delirium? . BMC Anesthesiol. 2012;12 (4):2253-9.

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects
			Measure	Outcome	
Kinjo 2012 **USA** **Setting** University Hospital **Study Design** prospective cohort study **Selection method** Patients whether had femoral nerve block **Study Length/Start-Stop Dates** 2001-2011 **Purpose** To compare the incidence of post-operative delirium between patients who had femoral nerve block for post-operative analgesia vs. those who did not. **Funding source(s):** NIH Grant [5RO1AG31795-03] **Quality Score** 3 **Risk of Bias**: High	**N = 88** n = 3 excluded (see below) **N = 85 in analysis** n=14 drop out The 14 patients with incomplete delirium assessment or preoperative TICS score due to patients refusal or medical condition. There was *no significant difference* between patients with missing vs without missing data in all in all variables **Inclusion** >65 yrs Surgery for unilateral total knee replacement (TKR) Informed consent **Exclusion** n = 3 2 postoperative epidural infusion 1 femoral and sciatic nerve blocks Not able to speak English No written informed consent Moderate to severe dementia Postop epidural catheter **Population selection source (s)** Part of a larger study examining the pathophysiology of postoperative delirium conducted from 2001-2011 at the UC San Francisco Med Ctr. **Preoperative assessment (all patients):** (Anesthesia clinic <2 weeks before surgery by a trained RA who also conducted postoperative assessments) Interview (baseline demographics) Hx CNS disorders Daily alcohol consumption Physical exam Use of benzodiazepines Use of opioids Preoperative pain level -Numeric Rating Scales (NRS) Cognitive status (by telephone) -Telephone Interview for Geriatric Depression Scale (GDS)	**n = 31 continuous femoral nerve block** Men 13 (42%) Mean age 72.8 ± 5.8 White: 23 (74%) Less than college 12 (40%) College or above 18 (60%) History of CNS disorders 18 (58%) Continuous femoral nerve block ± patient controlled analgesia Received either general anesthesia with inhalational agents or spinal anesthesia with single shot femoral nerve block with local anesthetic (e.g., 30 ml of 0.5% ropivacaine) followed by continuous local anesthetic infusion in the femoral nerve catheter The anesthesia team performed sensory and motor testing of the femoral nerve block immediately before surgery	**Delirium assessment:** Confusion Assessment Method (CAM) **Baseline characteristics** ASA >3 **Primary outcomes** Delirium on POD1 or POD2 *Predictive variables for postoperative delirium* Pain management Preoperative TICS score **Secondary outcomes** Length of hospital stay Altered sleep-wake cycle d1 Pain at rest on POD 1 Change in pain level POD 1 Benzodiazepine use on POD 1 Hydromorphone dose d1	On postop days 1-2, the same trained RA conducted structured interviews daily, that included the CAM, NRS (pain), use of pain meds, sleep-wake cycle and post-op benzodiazepine use; delirium severity were not discussed. **Femoral Block + PCA (31) vs PCA only (54)** No significant difference between groups except: 23 (74%) vs 25 (46%), p=0.01 7 (25%) vs 31 (61%), p= 0.002 OR 7.02 (2.06-23.97), p = 0.002 OR 0.87 (0.77-0,98), p = 0.03 5.7 ± 6.4 vs 5.0 ± 1.9 , p=0.58 10 (33%) vs 25 (49%), p= 0.17 4.6 ± 3.0 vs 4.5 ± 2.9, p= 0.89 0.9 ± 3.2 vs 1.9 ± 3.7, p= 0.20 2 (6%) vs 9 (17%), p= 0.18 4.3 ± 4.6 vs 5.9 ± 6.1, p= 0.24	**Comments:** This study showed femoral nerve block reduced the rate of delirium. The current findings did show that the use of femoral nerve block reduced the amount of intraoperative opioid dose, but the opioid sparing effect did not appear to extend to the postoperative opioid. The reduced intraoperative opioid use is likely related to the bolus of local anesthetic administered for femoral nerve block during the catheter placement. Pain assessment was conducted once daily during the patient interview. Because acute postoperative pain is dynamic and may fluctuate, we may not have evaluated the complex relationship between postoperative pain and delirium completely.
		n = 54 patient-controlled analgesia (PCA) Men 23 (43%) Mean age 74.5 ± 6.5 White: 39 (72%) Less than college 29 (56%) College or above 23 (44%) History of CNS disorders 35 (67%) PCA analgesia only Received general or regional block (spinal or epidural) followed by intravenous PCA analgesia. The epidural catheter was discontinued in the Post Anesthesia Care Unit (PACU) before the patient was transferred to the floor.	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Secondary outcomes**	See above See above See above See above	

Conclusion: Femoral nerve block reduces the incidence of postoperative delirium. These results suggest that a larger randomized control trial is necessary to confirm these preliminary findings.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	more patients classified as ASA>3 in the femoral nerve block group
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	NA – observational study
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	NA – observational study
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	Unclear	Drop out 14/85 >10%; dropouts analyzed with included patients, but 3 excluded patients not analyzed
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	1	Low	
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	0		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 3**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G4- Hakim SM, Othman AI, Naoum DO. Early treatment with risperidone for subsyndromal delirium after on-pump cardiac surgery in the elderly: a randomized trial. Anesthesiology. 2012;116(5):987-97.

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects
			Measure	**Outcome**	
Hakim 2012 **Egypt** **Setting** University hospital **Study Design** A randomized, double-blind, placebo-controlled, parallel-arm study **Randomization method** Randomization was carried out by a clinical pharmacist using a computer-generated random number list created with GraphPad StatMate v.1.01i software using permuted blocks of size 4. **Study Length/Start-Stop Dates** 12/2007 – 11/2010 **Purpose** To evaluate the effect of treating subsyndromal delirium (SSD) with risperidone on the incidence of clinical delirium in elderly patients who underwent on-pump cardiac surgery. **Funding source(s):** Support was provided solely from institutional and/or departmental sources. **Quality Score** = 8 **Risk of Bias**: Low	**N = 101** n = 51 intervention n = 50 **Inclusion** >65 yr Undergoing on-pump cardiac surgery No history of neuropsychiatric disorders, alcoholism, substance abuse, or intake of psychotropic medications. With SSD (ICDSC 1-3) **Exclusion** **N= 142** 19 Declined to participate 47 Not meeting inclusion criteria 76 Not meeting criteria for SSD **Exclusion criteria:** MMSE<25 GDS >4 Impaired hearing or visual acuity Speech difficulty Contraindication to risperidone or haloperidol Hx of neuroleptic malignant syndrome, Prolonged QTc syndrome Hx cerebrovascular disease other noncardiac procedures **Assessment of SSD:** Screening SSD using the Intensive Care Delirium Screening Checklist (ICDSC): physician who were trained systematically assessed 4 h after extubation and each 8-h nursing shift. Define SSD as ICDSC score of 1–3. **All patients protocol:** standardized balanced anesthetic technique, cardiopulmonary bypass, and a standard protocol was implemented for sedation, analgesia, and management of mechanical ventilation after surgery (see PDF).	**n = 51 risperidone 0.5 mg q12h po.** Men/women = 33/18 Age: 65 to 70 yr 36 (70.6%) >70 yr 15 (29.4%) **Intervention** The test drugs were continued for 24 h after subsidence of SSD (0 on the ICDSC) or until ICDSC >3. Patients who experienced delirium, the dose of risperidone was incrementally increased until symptoms were controlled or attained dose of 4 mg/d. **n = 50 placebo q12h po.** Men/women = 36/14 Age: 65 to 70 yr 39 (78%) >70 yr 11 (22%) **Intervention** (see above) Patients in the placebo group who experienced delirium were given 0.5 mg oral risperidone every 12 h, and if symptoms were not controlled, the dose could be increased to 4 mg/d. In either group, haloperidol was used as a second line rescue medication if symptoms were not controlled with risperidone in a daily dose of 4 mg. Haloperidol was begun orally at 0.5 mg q8h and could be escalated to 10 mg/d if needed. Rescue medications were started once the diagnosis of delirium was confirmed, and the dosage could be escalated by doubling the dose at 24-h intervals, if needed, until symptoms were controlled or the maximum dosage limit was attained. Rescue medications were continued for 24h after a score of 0 was achieved on the ICDSC.	**Delirium assessment:** Statistical Manual of Mental Disorders (DSM) **SSD assessment:** **Provide baseline zharacteristics/measures** Demographic and Pre-op Data - MMSE score (28-30) - MMSE score (25-27) -GDS (0-2) -GDS (3-4) Operative and Post-op Data -post-op intubation >24 h ICDSC score 1 ICDSC score 2 ICDSC score 3 **Primary outcomes:** Possibly delirious: ICDSC >3 Incidence of delirium (DSM) Absolute risk reduction Number needed to treat **Secondary outcomes:** Duration of delirium Need for haloperidol Highest doses of risperidone Highest doses haloperidol Highest score on the ICDSC Length of ICU LOS Extrapyramidal side effects **Adjusted analysis:** Failure to treat SSD with risperidone Rudolph Risk Score	If ICDSC >3, psychiatrist confirmed delirium using DSM criteria no inter-rater reliability, no cognitive testing done, no other details described. **See population column** ***Risperidone vs Placebo*** No significant difference 30 (58.8%) vs 31 (62%) 21 (41.2%) vs 19 (38%) 25 (49%) vs 26 (52%) 26 (51%) vs 24 (48%) No significant difference 5 (9.8%) vs 3 (6%) 19 (37.3%) vs 17 (34%) 17 (33.3%) vs 17 (34%) 15 (29.4%) vs 16 (32%) 8 (15.7%) vs 19 (38%), p =.011 7 (13.7%) vs 17 (34%), p =.031 0.20 (95% CI, 0.04 – 0.37) 4.9 (95% CI, 2.7–24.4) 3 (2 to 4) vs 3 (3 to 4) p=.664 2 (28.6%) vs 3 (17.6%) p=.608 3 (2 to 4) vs 3 (2.25 to 3.5) p=.318 0 (0 to 1.5) vs 0 (0 to 0) p=.757 6 (5 to 7) vs 5 (4 to 5) p=.234 2 (2 to 3) vs 3 (2 to 3) p=.517 6 (5 to 7) vs 6 (5 to 8) p=.056 2 (3.9%) vs 1 (2%) p=1.0 3.83 (95% CI, 1.63– 8.98; P=.002) 2.62 (95% CI, 1.51– 4.53; P=.001)	*Risperidone vs Placebo* **Extrapyramidal:** 2 (3.9%) vs 1 (2%); P=1.0 **Death:** 2 (3.9%) vs 1 (2%) **Mechanical ventilation:** 3 (5.9%) vs 2 (4%) **Second operation:** 1 (1.96%) vs 2 (4%) **Abnormality of the QTc interval and emergency breaking of the concealment envelopes** 0 vs 0 **Comments:** The current study showed that 57.1% of patients experienced SSD after surgery. The incidence of clinical delirium observed in the current study was 23.8%. Neither the ICDSC nor the CAM-ICU has been validated for severity scoring of delirium, so the highest score on the ICDSC was reported in the current study as a measure of severity, taking advantage of the ordinal framework of this scale. it is probable that the study had low power to detect a statistically significant difference between the two groups with regard to ICU, hospital length of stay, duration of delirium, highest score on the ICDSC, or consumption of antipsychotic medications.
Conclusion: Using risperidone in elderly patients who experienced subsyndromal delirium after onpump cardiac surgery was associated with significantly lower incidence of delirium.					

QUALITY / RISK OF BIAS

RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score** **1 or 0 [include notes for any 0s]**	**Risk of Bias Rating** **(Low; Unclear, High)** **[include notes on interpretation]**	**Notes for** **0 Quality Scores and** **Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	1	Low	
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study o For observational studies: confounders inadequately controlled o For RCT, lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	1	Low	Based on the intention to treat.
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = Low**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 8**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G4-Girard TD, Pandharipande PP, Carson SS, et al. .Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: the MIND randomized, placebo-controlled trial. Crit Care Med. 2010;38(2):428-37.

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects
			Measure	**Outcome**	
Girard 2010 **USA** **Setting** Multicenter – 6 tertiary care medical centers **Study Design** Randomized, double-blind, placebo-controlled trial. **Randomization method** Computer-generated, permuted block randomization scheme stratified according to study center. **Study Length/Start-Stop Dates** 21-day study period 2/2005 – 7/2007 **Purpose** To demonstrate the feasibility of a placebo-controlled trial of antipsychotics for delirium in the intensive care unit and to test the hypothesis that antipsychotics would improve days alive without delirium or coma. **Funding source(s):** NIH HL007123, the Hartford Geriatrics Health Outcomes Research Scholars Award Program, the Vanderbilt Physician Scientist development Program, and GRECC. **Quality Score** 6 **Risk of Bias**: Unclear	**N = 103 randomized and analyzed** n = 35 haloperidol n = 30 ziprasidone n = 36 placebo **Inclusion** >18 yrs ICU patients had abnormal level of consciousness or were receiving sedative or analgesic medications **Exclusion** N =3194 1000 neurologic injury 536 high risk of VT 344 ventilated >60 hrs 190 had no gastric access 174 post-suicide attempt 108 used neuroleptics 107 severe dementia 44 post-liver transplant 19 pregnant 16 neuroleptic allergy 247 enrolled in other study 210 no informed consent **All patients protocol:** The second dose of study drug was administered 12 hrs after if QTc interval >500 msec; and then q6h. Study drug frequency was reduced to every 8 hrs when patients were two consecutive negative for CAM-ICU. Reduced to every 12 hrs when patients were delirium/coma-free on three consecutive assessments, and discontinued when patients were delirium/coma-free on four consecutive assessments. Blood was collected from each patient within 48 hrs of study drug initiation.	**n =35 haloperidol every 6 hrs x 14 days** n = 2 discontinued protocol n = 2 withdrew **n = 35 analyzed** Female, 15 (43%) Mean age 51 (35–59) 5 mg haloperidol (as a solution containing 1 mg/mL) **n = 30 ziprasidone every 6 hrs x 14 days** n = 0 discontinued/ withdrew **n = 30 analyzed** Female, 9 (30%) Mean age 54 (47–66) 40 mg ziprasidone (as a solution containing 8 mg/mL) **n =36 placebo every 6 hrs x 14 days** n = 2 discontinued n = 1 withdrew n = 1 received EoL care **n = 36 analyzed** Female, 14 (39%) Mean age 56 (43–68) placebo (as a 5-mL solution)	**Delirium assessment:** Confusion Assessment Method for the ICU (CAM-ICU) RASS **Baseline measures** APACHE II score Brain dysfunction -Delirium -Coma Haloperidol before enrollment Ziprasidone before enrollment **Primary outcomes** Delirium/coma-free days **Secondary outcomes** ventilator-free days hospital length of stay 21-day mortality Average extrapyramidal symptoms score Daily delirium risk Study drug delivery and other antipsychotics	CAM-ICU rated by trained RAs twice daily based on RASS. Inter-rater reliability was not discussed. **Haloperidol vs ziprasidone vs Placebo** No significant difference between groups 26 vs 26 vs 26 16 vs 15 vs 17 12 vs 9 vs 14 1 vs 2 vs 4 0 vs 0 vs 0 **Haloperidol vs ziprasidone vs Placebo** 14.0 (6.0–18.0) vs 15.0 (9.1–18.0) vs 12.5 (1.2–17.2) 7.8 (0–15.0) vs 12.0 (0–18.6) vs 12.5 (0–23.3) (p =0.25), 13.8 vs 13.5 vs 15.4 (p =0.68) 4 vs 4 vs 6 (p = 0.81). 0 (0–0.2) vs 0 (0–0) vs 0 (0–0) p=0.56 **Haloperidol vs ziprasidone (OR (CI), p)** 1.2 (0.6 –2.2) vs 1.1 (0.5–2.2),p= 0.80 No significant difference	**Haloperidol vs ziprasidone vs Placebo** *Akathisia:* 10 (29%) vs 6 (20%) vs 7 (19%) (p =0 .60) *Extrapyramidal symptoms* similar between treatment groups (p =0.46). **Comments:** This pilot study was designed primarily to demonstrate the feasibility of a double-blind, placebo controlled trial of antipsychotics for ICU delirium, it was likely significantly underpowered to demonstrate the potential efficacy for many outcomes including length of stay and survival. Limitations of the trial include the small sample size, lack of enforcement by study personnel of a standardized sedation protocol, and the exposure of some patients in the ziprasidone and placebo groups to open-label haloperidol.

Conclusion: A randomized, placebo-controlled trial of antipsychotics for delirium in mechanically ventilated intensive care unit patients is feasible. Treatment with antipsychotics in this limited pilot trial did not improve the number of days alive without delirium or coma, nor did it increase adverse outcomes.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	1	Low	
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study o For observational studies: confounders inadequately controlled o For RCT, lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Sponsored by Pfizer, Inc., No ITT, but all randomized were analyzed
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = Unclear**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	0		Each group around 35
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 6**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G4 Devlin JW, Roberts RJ, Fong JJ, et al. Efficacy and safety of quetiapine in critically ill patients with delirium: a prospective, multicenter, randomized, double-blind, placebo-controlled pilot study. Crit Care Med. 2010;38(2):419-27.

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects
			Measure	**Outcome**	
Devlin 2010 **USA** **Setting** Three academic medical centers ICU **Study Design** RCT-double blind, placebo controlled **Randomization method** Assigned in blocks of four in a 1:1 ratio by means of a computer-generated random number table. **Study Length/Start-Stop Dates** 4/2006 – 8/2008 **Purpose** To compare the efficacy and safety of scheduled quetiapine to placebo for the treatment of delirium in critically ill patients requiring as-needed haloperidol. **Funding source(s):** Supported, in part, by the Society of Critical Care Medicine's Joseph F. Dasta Critical Care Pharmacy Research Award and an unrestricted grant from AstraZeneca Pharmaceuticals. **Quality Score** 5 **Risk of Bias**: High	**N = 258 screened** n = 222 excluded (see below) **N = 36 included in analysis** n = 18 intervention n = 18 placebo Dropouts = 10/36 (27.7%) -1 recovered from delirium -2 placebo pts by ICU attending (severe agitation) -3 ICU discharge -4 adverse events **Inclusion** ICU patients with delirium - ICDSC score ≥4 Tolerating enteral nutrition No complicating neurologic condition. Informed consent **Exclusion** N = 222 48=Prior antipsychotic use in 30 d 38=receiving enteral nutrition 29=Primary neurological condition 16=Advanced liver disease 12=Alcohol withdrawal 12=Inability to conduct ICDSC 11=No delirium 11=Inability to obtain informed consent 10=Moribund 8=Irreversible brain disease 7=Current drug therapy w/agents affecting quetiapine concentrations 6=Current drug therapy with class Ia, Ic or III antiarrhythmics 5=Baseline QTc interval ≥500msec 5=Attending physician refusal for enrollment 7=Other	**n = 18 quetiapine 50~200mg q12h 10 days** Men and women (56%) Mean age = 62.4 (14) **Intervention** Study drug or placebo administered: Quetiapine was increased every 24 hrs (50 to 100 to 150 to 200 mg every 12 hrs) . Study drug was continued until the ICU team discontinued it because of delirium resolution, therapy ≥10 days, or intensive care unit discharge. All subjects were allowed to receive IV haloperidol 1 to 10 mg administered up to every 2 hrs if nurses observed delirium sx not resolved by study drug **Evaluation:** By trained critical care nurses: Sedation-Agitation Scale (SAS) every 4 to 6 hrs QTc interval at least every 12 hrs Signs of extrapyramidal symptoms by using the Simpson-Angus Scale within 1 hr then every 12 hrs	**Delirium assessment:** Intensive Care Delirium Screening Checklist (ICDSC)	Delirium assessments were completed at the subject's bedside formally educated critical care nurses at baseline and during every nursing shift. Duration: 10 days Inter-rater reliability and severity assessment not described.	More subjects treated with quetiapine (6 vs 2) experienced study drug related adverse events, but this did not reach statistical significance. 5 = somnolence 1 = hypotension No episodes of extrapyramidal symptoms QTc prolongation was similar in both groups **Comments** Limitations -small sample size -86% of screened patients excluded -minimum duration of study drug not required -duration of delirium may have been inaccurate -discontinuation of study drug may have been premature -"as needed" haloperidol used for all patients -greater use of haloperidol placebo patients could have diminished the observed treatment effect of quetiapine -did not formally assess dementia at baseline -short term safety goals may not have been evenly distributed (early termination of study drug) Future studies should assess -mortality -LOS ICU & hospital stay -post-ICU cognitive function -quality of life -ability to complete activities of daily living. -safety for longer duration -cost effectiveness
			Baseline characteristics	No significant difference between groups	
			Primary outcomes time to first resolution of delirium (days)	***Quetiapine vs placebo*** 1.0 [0.5–3.0] vs. 4.5 [2.0 –7.0]; p < .001	
			Secondary outcomes (see PDF) Time of study drug administration (hrs) Time in delirium -Hours -Percent Time spent agitated -Hours -Percent Home/rehabilitation center% Fentanyl -amount per day, ug -total - Percent Study drug -Daily dose, mg -Maximum daily dose, mg	***Quetiapine vs placebo*** 102 (84 -168) vs 186 (108 -228) p= .04 36 (12–87) vs 120 (60–195) p=.006 53 (16–67) vs 69 (58–100) p= .02 6 (0–38) vs 36 (11–66) p=.02 3 (0–22) vs 21 (8–41) p=.03 89 vs 56 p=.06 0 (0–65)vs 170 (14–1089) p=.02 0 (0–3)vs 4 (1–9) p=.03 0 (0–60)vs 70 (17–100)p= .07 110 (88–191) vs 210 (116–293) p=.01 200 (100–313)vs 375 (225–400) p=.02 NOTE: Schedule IV or oral haloperidol and other antipsychotic medications were not allowed during the study	
		n = 18 placebo 10 days Men and women (56%) Mean age = 63.6 (15.3) **Intervention** (see above)	**Delirium assessment:** **Baseline characteristics** **Primary and secondary outcomes**	See above See above See above	

Conclusion: Quetiapine added to as-needed haloperidol results in faster delirium resolution, less agitation, and a greater rate of transfer to home or rehabilitation.

QUALITY / RISK OF BIAS

RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score** **1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	1	Low	
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	High	Flow chart listing dropouts (27.7%) did not differentiate between intervention vs placebo
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present o	0	High	Possible confounders (see limitations) Drug company sponsorship of study (AstraZeneca) (ITT analysis done but low Nn)
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	0		36 total subjects
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 5**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G4-Tahir TA, Eeles E, Karapareddy V, et al. A randomized controlled trial of quetiapine versus placebo in the treatment of delirium. J Psychosom Res. 2010;69(5):485-90.

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects Comments
			Measure	Outcome	
Tahir TA 2010 **UK** **Setting** University Hospital **Study Design** RCT (double blind, placebo controlled) **Randomization method** Computer-generated randomization codes **Study Length/Start-Stop Dates** 6/ 2003 to 4/ 2005 **Purpose** To determine the efficacy and acceptability of quetiapine in the treatment of incident delirium in general hospital inpatients with or without minor pre-existing cognitive deficits. **Funding source(s):** AstraZeneca UK funded RA, trial medication and randomization codes **Quality Score** 4 **Risk of Bias**: High	**N = 342 screened** n = 257 no delirium/ excluded n = 115 delirium **N = 42 recruited and randomized** **Inclusion** With delirium (DRS-R-98>15) **Exclusion** N = 257 no delirium Score <15 on DRS No consent Severe physical illness Impairment of mental capacity Severe cognitive deficits Alcohol withdrawal Pre-existing psychosis Substance dependence Inability to comply with the constraints of the trial Contraindications to quetiapine **Assessments** Delirium Rating Scale Revised 98 (DRS-R-98) MMSE Brief Psychiatric Rating Scale (BPRS) Clinical Global Improvement (CGI) Abnormal Involuntary Movements Scale (AIMS) Medical record case notes **Follow up** A follow-up assessment was also undertaken on Day 30.	**n = 21 Quetiapine group** n = 5 discontinued -3 deaths -1 adverse events -1 doctor stopped med **n = 16 completed study** Men: 6 (28.6%) Mean: 84.1 (9.45) A flexible dosing regime of 25mg once daily oral quetiapine with dose titration of 25 mg/day to a maximum daily dose of 175 mg in divided doses. Dose increased only if DRS-R-98 and clinical condition did not show any improvement Dose down-titrated if symptoms improved as indicated by improvement in DRS-R-98	**Delirium assessment:** DSM-IV DRS-R-98 **Baseline characteristics** **Primary outcomes** DRS-R-98 Severity DRS-R-98 Total DRS-R-98 Cognitive DRS-R-98 Non-cognitive DRS-R-98 <15 on Day 7 Maximum dose of quetiapine **Secondary outcomes** MMSE D1 MMSE D3 MMSE D10 the Brief Psychiatric Rating Scale (BPRS) Clinical Global Improvement (CGI)	RA conducted screening daily using DSM IV criteria and DRS on medical, surgical and orthopedic wards. Patients with delirium (DRS score ≥15). Follow up on Days 1, 2, 3, 4, 7, and 10. No significant demographic or clinical difference between groups **Quetiapine vs Placebo** 0.827 (0.371, P=.026) 0.55 (0.285, P=.054) 0.572 (0.443, P=.197) 0.577 (0.292, P=.048) 18 (85.7%) vs 17 (80.9%) 40 mg 11.829 (4.080) vs 11.829 (4.080) 16.773 (3.838) vs 16.317 (3.689) 18.534 (4.757) vs 18.504 (4.739) Not reported Not reported	**Quetiapine vs Placebo** *Died within 30 days:* 4 vs 3 Deaths were considered to be related to underlying serious medical conditions rather than the study medication *Abnormal involuntary movements in 10 days:* 4.8% vs 14.3% *Dropouts (except for death):* *2 vs 5* One patient was withdrawn from quetiapine due to complaints of sedation. **Comments** The trial was stopped early at the request of the manufacturer due to FDA concerns on the use of antipsychotic medication in the elderly. A statistically significant improvement in noncognitive items including restlessness, agitation, thought disorder, and perceptual impairment on the DRS-R-98 was found on Day 3 with a mean dose of quetiapine lower than previously documented, possibly contributed to by the high mean age of 84 years. Due to the small sample size, this should be considered a pilot study.
		n = 21 Placebo group n = 7 discontinued -1 death -2 withdrew -1 noncompliance -1 aspiration risk -1 medication not given -cerebrovascular event **n = 13 completed study** Men: 6 (28.6%) Mean age: 84.3 (7.16) Matching placebo tablet	**Delirium assessment:** **Baseline characteristic** **Primary outcomes** **Secondary outcomes**	See above See above See above See above	

Conclusion: Quetiapine has the potential to more quickly reduce the severity of noncognitive aspects of delirium. This study was underpowered for treatment comparisons at specific points in time but nonetheless detected significant differences when analyzing the whole study period. While it is not possible to draw definitive conclusions, further larger studies exploring the use of quetiapine in other delirium populations seem justified. Larger increments in the dose of quetiapine may yield even stronger results.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	1	Low	
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	High	Discontinued 12/42 (28.6%)
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	0	High	Not reported: Brief Psychiatric Rating Scale (BPRS) and Clinical Global Improvement (CGI)
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	AstraZeneca UK sponsored and provided funding No ITT analysis
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	0		<50 total subjects
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 4**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G4- Maneeton B, Maneeton N, Srisurapanont M, Chittawatanarat K. Quetiapine versus haloperidol in the treatment of delirium: a double-blind, randomized, controlled trial. Drug Des Devel Ther. 2013;7(July):657-67.

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects Comments
			Measure	Outcome	
Maneeton 2013 **Thailand** **Setting** University hospital **Study Design** A 7-day prospective, double-blind, randomized controlled trial **Randomization** Using a computer-generated randomization system **Study Length/Start-Stop Dates** 7/2009 – 4/2011 **Purpose** To compare the efficacy and tolerability between quetiapine and haloperidol in controlling delirious behavior. **Funding source(s):** Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand, grant number 077/52. **Quality Score** 6 **Risk of Bias**: Unclear	**N = 408 screened** n = 356 excluded **N = 52 randomized and analyzed** n = 24 quetiapine n = 28 haloperidol **Inclusion** 18–75 yr Delirium (DSM-IV-TR, CAM) **Exclusion criteria:** Substance-induced delirium Known allergy Intolerance to test medicine Pregnancy or breast feeding Being on an antipsychotics Renal or hepatic failure **Exclusion** **N= 356** 153 Alcohol withdrawal delirium 80 Received antipsychotics 79 <18 or>75 yrs 16 Primary doctors did not allow 15 Renal or hepatic failure 5 cannot communicate 2 Hypoactive delirium 2 Inability to obtain consent 2 Seizures 2 Disallowance for medication **All patients protocol:** Orally administered a flexible dose of quetiapine (25–100 mg/d) or haloperidol (0.5–2.0 mg/d) before bedtime and as needed. Adjusted the doses based on the clinical safety, sleepiness, and calmness as measured by the DRS-R-98. For all participants, started the study medication by giving one capsule orally at bedtime and giving one more capsule every 2–3 hrs for agitation. The maximum dose was four capsules per 24 hrs. Other psychotropic medications, including benzodiazepines, were prohibited.	**n = 24 quetiapine 25 mg po.** n = 13 completed 7 days of therapy Dropouts = 10 4 = discharged 2 = adverse events 2 = early stop medication 1 = receiving other antipsychotic 1 = inefficacy 1 = died Male (%) : 15 (62.5%) Mean age: 56.6 (12.0) **Intervention** The test drugs were continued for 24 h after subsidence of SSD (0 on the ICDSC) or until ICDSC >3. Patients who experienced delirium, the dose of risperidone was incrementally increased until symptoms were controlled or attained dose of 4 mg/d. **Daily assessment:** Total sleep time per day Clinical Global Impression–Improvement (CGI–I) Modified (nine-item) Simpson–Angus Scale (MSAS) Response and remission rates (defined as a reduction of the DRS-R-98 severity score from baseline for ≥50% and a DRS-R-98 severity score of 12 or less without relapse.) **n = 28 haloperidol 0.5 mg po.** n = 22 completed 7 days of therapy Dropouts = 5 3 = discharge 1 = adverse events 1 = inefficacy 1 = died Male (%): 20 (71.4) Mean age: 57.0 (11.9) **Intervention** (see above) .	**Delirium assessment:** Confusion Assessment Method (CAM) DRS-R-98 **Baseline characteristics** Education **Primary outcomes:** Duration (days) of delirium Change in DRS-R-98 severity score **Secondary outcomes:** DRS-R-98 noncognitive scores DRS-R-98 cognitive scores response rate remission rate Time to first remission Increase in total time of sleep CGI–I scores improvement.	Frequency: CAM and DRS R 98 (severity) daily in the evening (5 pm–10 pm). Rater: investigator Duration: 7 days Inter-rater reliability not described No significant difference between groups > 50% fewer than 6 yrs 3.3 (2.5) vs 2.9 (2.8), p=.16 −22.9 (6.9) vs −21.7 (6.7), p=.59 −16.9 (5.5) vs −15.8 (4.7); p=.54 −6.0 (3.2) vs −5.8 (3.6); p =.89 79.2% vs 78.6%,p =.97 2.6 (1.9) vs 1.8 (1.5), p=.14 HR 1.15 (0.6-2.19), p=.68 6.5 (3.0) vs 6.1 (3.4), p =.74 -1.1 (1.0) vs -1.2 (1.4), p=.96	extrapyramidal side effects were assessed by MSAS. ***Quetiapine vs haloperidol*** **Completed 7 ds therapy** 13 (54.2%) vs 22 (78.6%) **MSAS scores:** 0.3 (0.7) vs 0.3 (1.1) P=.51 **Hypersomnia:** 10 (41.7) vs 8 (28.6),p=.32 **Tremor:** 0 (0) vs 1 (3.6), p=1.00 **Nightmare:** 1 (4.2) vs 0 (0), p=.46 **Rash:** 1 (4.2) vs 1 (3.6), p=1.00 **Akathisia:** 0 (0) vs 1 (3.6), p=1.00 **TICS:** 0 (0) vs 1 (3.6), p=1.00 Discharge (n = 4 vs 5) Adverse events (2 vs 3) Early stop med (2 vs 1) Receiving other antipsychotics (1 vs 1) Inefficacy (1 vs 1) Death (1 vs 1) (not study drug related) **Comments** In this study, the average dose of anti-psychotics in the management for delirium was relatively low compared with those applied in previous studies. As vulnerable subjects, the delirious patients aged over 75 and severely ill, eg, with renal or hepatic failure, were excluded.
Conclusion: Low doses of both quetiapine and haloperidol are equally effective and safe for the management of behavioral disturbance in delirious patients.					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	1	Low	
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	High	Drop out 15/52 (29%)
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study o For observational studies: confounders inadequately controlled o For RCT, lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	1	Low	
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = Unclear**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	0		Total sample: 52
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 7**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G4-Han CS, Kim YK. A double-blind trial of risperidone and haloperidol for the treatment of delirium.Psychosomatics. 2004;45(4):297-301..

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects
			Measure	Outcome	
Han 2004 **Korea** **Setting** University hospital **Study Design** A randomized, double-blind trial **Randomization method** A consulting psychiatrist (non-investigator) randomly assigned patients ; patients, caretakers and psychiatrist who rated symptoms did not know the drugs prescribed **Study Length/Start-Stop Dates** 7 days **Purpose** To compare the clinical efficacy of risperidone with haloperidol for the treatment of delirium. **Funding source(s):** Brain Korea 21 Project **Quality Score** = 5 **Risk of Bias**: High	**N = 28** n = 4 drop out n = 24 complete the study **Inclusion** With altered mental status Referred to the consulting psychiatry division **Exclusion** **N= not described** Dementia Other psychiatric diagnosis Used antipsychotics or benzodiazepines before study Cannot communicate verbally	**n = 12 haloperidol for 7 days (flexible dose; initial dose = 0.75 mg)** Men/women = 7/5 Mean age: 66.5 (15.9) **Intervention** A flexible-dose regimen. The initial starting dose of each drug was 0.75 mg (haloperidol) or 0.5 mg (risperidone) twice a day. The dosage was increased depending on the status of delirium during the 7 days. **n = 12 risperidone for 7 days (flexible dose; initial dose = 0.5 mg)** Men/women = 6/6 Mean age: 65.6 (8.3) **Intervention** (see above)	**Delirium assessment:** Confusion Assessment Method Delirium Rating Scale (DRS) Memorial Delirium Assessment Scale (MDAS) **Baseline characteristics** Medical diagnoses - Fractures -Cerebrovascular accident -Peritonitis -Chronic renal failure -Cancer -Cardiovascular disease -Other **Primary outcomes:** DRS MDAS response to the drugs average periods before response	Rating of CAM based on DRS at baseline. psychiatrist rated MDAS at the same time daily for 7 days. Inter-rater reliability was not discussed. MDAS for delirium severity ***Haloperidol vs Risperidone*** No significant differences 3 vs 4 3 vs 2 1 vs 1 1 vs 2 1 vs 1 2 vs 1 1 vs 1 21.83 (4.43) vs 23.50 (4.19), p=0.35 no significant difference p=0.51 9 vs 5, p=0.11 4.22 (2.48) vs 4.17 (2.14), p=0.95 Delirium Assessment Scale scores of each group decreased significantly during the study period ($p<0.05$); but there is no significant difference in the efficacy or response rate between haloperidol and risperidone.	None of the 24 subjects showed clinically significant side effects. One patient in the haloperidol group showed mild symptoms of akathisia but was able to tolerate this for the duration of the study.
Comments: The author thought differences might exist between Asian and non-Asian populations in the pharmacokinetics of psychotropic agents. Thus, the effective doses might be lower than those given to Caucasian patients.					
Conclusion: There were no significant differences in efficacy or response rate between haloperidol and risperidone among patients with delirium. Although a larger study might find significant differences it can be cautiously suggested that risperidone is not superior to haloperidol for the acute treatment of delirium.					

QUALITY / RISK OF BIAS

RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score** **1 or 0 [include notes for any 0s]**	**Risk of Bias Rating** **(Low; Unclear, High)** **[include notes on interpretation]**	**Notes for** **0 Quality Scores and** **Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	.
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	1	Low	
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	High	Drop out 4/28 (14%) Dropouts not described
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study o For observational studies: confounders inadequately controlled o For RCT, lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	No ITT analysis
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	0		Only 12 patients each arm
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 5**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G4- Grover S, Kumar V, Chakrabarti S. Comparative efficacy study of haloperidol, olanzapine and risperidone in delirium. J Psychosom Res. 2011;71(4):277-81.

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects
			Measure	**Outcome**	
Grover 2011 **India** **Setting** Academic hospital **Study Design** single-blind randomized controlled trial **Randomization method** computer-generated randomization table **Study Length/Start-Stop Dates** Not described **Purpose** To assess the efficacy and safety of second-generation antipsychotics olanzapine and risperidone vs. haloperidol in patients of delirium admitted to medical and surgical wards. **Funding source(s):** Institute Research Fund. **Quality Score**: 4 **Risk of Bias**: High	**N = 74** n = 10 drop out n= 64 analyzed **Inclusion** >18 yrs Diagnosis of delirium based on DRS-R98 and CAM **Exclusion** N =41 5 Alcohol/benzodiazepine withdrawal 2 Dementia 7 Terminal illness 3 Comorbid primary psychiatric illness 5 QTc interval >500 ms 3 Parkinson;s disease 16 no informed consent **All patients protocol:** The doses were titrated after daily clinical assessment; however, if the patient was agitated, titration was also done more than once per day. Side effects were rated on the Simpson Angus Scale, Abnormal Involuntary Movement rating scale (AIMS) and Udvalg for Kliniske Undersogelser (UKU) side effect rating scale Besides test medications, any medication that can cause delirium and/or was not essential for the care was discontinued. The etiological causes identified for delirium were treated with appropriate measures.	**n = 20 haloperidol 0.25 to 10 mg** Male/Female: 13/7 Mean age 44.09±16.84 Started on haloperidol 0.25 mg twice or thrice daily, gradually increased according to the necessity, most with 1.5 to 2.5 mg daily. 1.25 to 2.5 mg iv and repeat when patient is agitated **n = 21 risperidone 0.25 to 4 mg** Male/Female: 14/7 Mean age 45.39±19.18 Started on 0.25 to 0.5 mg/day, dose increased according to requirement, most patients require 0.5 to 1.5 mg/day. **n = 23 olanzapine 1.25 to 20 mg** Male/Female:, 18/5 Mean age 46.50±14.51 Started 1.25 to 5 mg/day, most patients require 1.25 to 7.5 mg/day. 2.5 to 5 mg/day if used in parenteral form.	**Delirium assessment:** Confusion Assessment Method (CAM) DRS-R98 **Baseline characteristics** (no significant difference) Education (yrs) Duration of delirium prior to assessment (h) DRS-R98 scores (d0) MMSE scores (d0) **Primary outcomes** **DRS-R98** -Day 3 -Day 6 DRS-R98 >10 on day 3 DRS-R98 >10 on day 6 **Secondary outcomes** **MMSE** -Day 3 -Day 6	CAM rated by RA based on MSSE on baseline. Inter-rater reliability was not discussed. DRS-R98 for delirium severity. **Haloperidol vs risperidone vs olanzapine** 8.09±3.28 vs 8.00±3.95 vs 9.35±3.54 41.71±22.96 vs 64.00±60.51 vs 77.20±58.96 21.85±4.77 VS 22.56±4.49 VS 23.80±5.16 6.38±5.02 vs 9.72±6.30 vs 6.84±5.33 **Haloperidol vs risperidone vs olanzapine** N = 20 vs 21 vs 21 10.14±6.35 vs 11.65±7.24 vs 11.95±6.82 (P=.43) 6.09±7.19 vs 9.17±8.65 vs 8.00±7.27 (P=.424) 12 (57.14%) 14 (60.86%) 12 (60%) (P=.967) 17 (81%) vs 16 (69.56%) vs 14 (70%) (P=.636) 17.90±7.37 vs 17.77±7.53 vs 17.57±6.22 (P=.989) 21.71±7.66 vs 20.77±8.14 vs 22.31±6.63 (P=.804)	**Haloperidol vs risperidone vs olanzapine** *Total number of subjects who had side effects* *4 vs 2 vs 6* **Dropouts** Haloperidol = 6 -2 shifted to ICU -2 comatose -1 LAMA (left hospital AMA) Risperidone =1 -1 LAMA Olanzapine = 3 -1 shifted to ICU -1 comatose -1 LAMA **Comments:** The sample predominantly composed of young adult subjects (<65 years) This study limited by the small sample size, and did not include a placebo control arm. In addition, the sample only included those subjects who were referred to consultation liaison psychiatric services, and the treating physician was not blind to the drug.
Conclusion: Risperidone and olanzapine are as efficacious as haloperidol in the treatment of delirium					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	Unclear	Not described
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	1	Low	
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	High	Drop out: 10/74 (13.5%)
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study o For observational studies: confounders inadequately controlled o For RCT, lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Did not use ITT analysis
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	0		Each group <30
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 4**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G4-Kim SW, Yoo JA, Lee SY, et al. Risperidone versus olanzapine for the treatment of delirium. Hum Psychopharmacol. 2010;25(4):298-302.

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects
			Measure	Outcome	
Kim 2010 **Korea** **Setting** University hospital **Study Design** Randomized, comparative clinical trial **Randomization method** Not described in detail; recruitment from patients who met inclusion criteria **Study Length/Start-Stop Dates** 12/2007 – 11/2010 **Purpose** To compare the effectiveness of risperidone and olanzapine in the treatment of delirium. **Funding source(s):** Grant (CRI08019-1) of the Chonnam National University Hospital Research Institute of Clinical Medicine. **Quality Score** 3 **Risk of Bias**: High	**N = 32** n = 17 risperidone n = 15 olanzapine **Inclusion** Delirium patients (by DSM-IV) **Exclusion** **N= not described** Dementia Serious hepatic problems Bone marrow suppression Taken antipsychotics Undergoing intubation Cannot communicate verbally **All patients protocol:** All outcome measures were evaluated at the same time every day for 7 days. Blinded investigators assessed daily, without recognizing the study medication. The initial starting dose was based on age, medical condition, and delirium severity, and the dosage was increased over 7 days, depending on the delirium status. Strict prohibition of rescue medication in patients with poor physical status would have produced ethical conflicts; therefore, rescue IM injection of haloperidol or benzodiazepine was permitted and recorded as an outcome variable.	**n = 17 risperidone 7 days** n = 12 (70.6%) completed study Men and women: (53%) Mean age: 66.7 (12.1) **Intervention** The mean starting dose was 0.6 +−0.2 mg/day risperidone (range, 0.25–1 mg/day) The mean dose at last observation was 0.9+-0.6 mg/day risperidone (range, 0.25–2 mg/day) **n = 15 olanzapine 7 days** n = 8 (53.3%) completed study) Men and women (60%) Mean age: 68.3 (10.7) **Intervention** The mean starting dose was 1.8+-0.6 mg/day olanzapine (1.25– 2.5 mg/day). The mean dose at last observation was and 2.4+-1.7 mg/day olanzapine (1.25–7.5 mg/day).	**Delirium assessment:** Delirium Rating Scale-Revised-98 (DRS-R-98) **Baseline characteristics** **Primary outcomes:** DRS-R-98 score **Secondary outcomes:** Response rate -Total Age ≥ 70 yrs Age <70 yrs Median time to response (d)	Frequency: Evaluated at the same time every day. Rater: Blinded investigators Duration: 7 days Inter-rater reliability not discussed No significant difference between groups in demographic or clinical characteristics ***Risperidone vs Olanzapine*** 25.8 (5.2) vs 23.5 (5.1) p=.217 64.7% vs 73.3%; p=.712 33.3% vs 70%; p=.024 100% vs 80% 5 vs 3; p=.298	**Drop outs:** n = 10 discharge from hospital n = 2 withdrawal of consent ***Risperidone vs olanzapine*** ***N = 13*** Tremor and bradykinesia n = 2 (11.8%) vs 1 (6.7%) Exacerbation of daytime somnolence or increased duration of sleep n = 5 (29.4%) vs 5 (33.3%), p=1.000) All extrapyramidal symptoms were tolerable and mild to moderate. **Comments:** These doses were relatively low compared with those in previous studies of risperidone and olanzapine. A more rapid and higher increase in the drug dose might have increased the efficacy of the study medications in the treatment of delirium, although the response rates in our study were not much different from those in previous studies. The limitation s of this study are small sample size and factors such as the use of rescue injections that cannot be strictly controlled.
Conclusion: Risperidone and olanzapine were equally effective in reducing delirium symptoms. The response to risperidone was poorer in the older age group.					

QUALITY / RISK OF BIAS

RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score** **1 or 0 [include notes for any 0s]**	**Risk of Bias Rating** **(Low; Unclear, High)** **[include notes on interpretation]**	**Notes for** **0 Quality Scores and** **Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	Not described
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	Reported: "rater blind study design: "psychiatrists randomly assigned patients". No other blinding described
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	High	Drop out 12/32 (37.5%)
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study o For observational studies: confounders inadequately controlled o For RCTs, lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	Unclear	"main analyses performed on modified ITT basis" but Very high dropout (37.6%)
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	0		Total N= 32
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 4**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G4-Skrobik YK, Bergeron N, Dumont M, Gottfried SB. Olanzapine vs haloperidol: treating delirium in a critical care setting. Intensive Care Med. 2004;30(3):444-9..

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects Comments
			Measure	Outcome	
Skrobik YK 2004 **Canada** **Setting** Tertiary care university affiliated critical care unit **Study Design** Prospective randomized trial **Randomization method** Randomized based on even vs odd date **Study Length/Start-Stop Dates** 7/2000 – 9/2001 **Purpose** To compare the safety and estimate the response profile of olanzapine, a second-generation antipsychotic, to haloperidol in the treatment of delirium in the critical care setting. **Funding source(s):** Grant from the Zyprexa fund, Eli-Lilly, North America **Quality Score** 1 **Risk of Bias**: High	**N = 1009 admitted to ICU** **N = 214 delirium dx** n = 111 excluded (see below) **N = 103 eligible for randomization** **N = 80 provided informed consent** n = 7 dropouts 3 = treating physician withdrew patient 2 = status changed to "no active treatment) 1 = drug interaction suspected 1 = data was lost **N = 73 in analysis analysis** **Inclusion** Age 18–75 yrs Admitted to ICU >24 hrs Delirium dx Informed consent **Exclusion** N = 111 (exclusions were due primarily to gastrointestinal dysfunction preventing oral/enteral administration) Pregnant Antipsychotics within 10 days before admission Test drug were contraindicated Parkinson's disease Oropharyngeal dysfunction Prolonged QT interval Hepatic or renal dysfunction Gastrointestinal dysfunction precluding oral/enteral drug administration Neurological condition preventing neuropsychiatric evaluation **Assessments** Acute Physiology and Chronic Health Evaluation (APACHE II) Daily worst Ramsay score Extrapyramidal signs assessed with Ross-Chouinard and Angus-Simpson scales by a physician	**n = 45 haloperidol group** Men and women: 31% Mean age 63.26 (11.66) Haloperidol was initiated at 2.5–5 mg every 8 h Daily dose 6.5 mg (range 1– 28 mg) **Protocol for all patients:** The intensivist prescribed the antipsychotic orally or via enteral tube within 2 h of the diagnosis of delirium. Patients over 60 years received a lower initial dosage (haloperidol 0.5–1 mg, or olanzapine 2.5 mg). Subsequent titration was based on clinical judgment.	**Delirium assessment:** ICU Delirium Screening Checklist (ICU-DSC) Delirium index (DI) DSM IV **Baseline characteristics** Age **Outcomes** daily DI scores Time effect Group effect and interaction effect Dose of benzodiazepines Time effect Group and interaction effect Dose of rescue haloperidol, opiates or sedatives (other than BZD)	Daily rating ICU-DSC by a clinician or research nurse; physician determined if DSM IV criteria met. DI for delirium severity daily. Overall agreement regarding DI scores CCI = 0.96. Significant difference between groups 63.26 (11.66) vs 67.50 (6.04) p = .05 **All patients** 7.08 (day 1) to 5.05 (day 5) NS P = .02 NS (see Fig 1) NS (lorazepam equivalents) P = .02 NS (See Fig 2) NS (no figure or specific data)	**Haloperidol vs Olanzapine** extrapyramidal symptom testing 6 rated low scores vs 0 No patient in either group received prophylactic or therapeutic antiparkinsonian therapy. There were no adverse effects (specific or otherwise) attributable to olanzapine. **Comments** Both olanzapine and haloperidol were effective in reducing delirium symptoms. The clinical course in both treatment arms was unmarred by severe agitation. Intravenous rescue haloperidol, used in the first 24 h in both groups, may have contaminated the early DI evaluation between the groups. Given the reported half life of intravenous haloperidol, however, and the small number of patients who required it beyond the first day, it is unlikely the overall beneficial evolution of the olanzapine group over time is attributable to the rescue haloperidol received on the first day. There was uneven distribution between the two treatment groups. The odd/even day randomization, chosen for convenience, was not corrected for the slightly more frequent occurrence of odd days on which patients were randomized to receive haloperidol in this study.
		n =28 olanzapine group Men and women: (21%) Mean age : 67.50 (6.04) Olanzapine was begun at 5 mg daily 4.54 mg for the olanzapine group (range 2.5–13.5 mg) **Protocol for all patients:** See above	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Secondary outcomes**	See above See above See above See above	

Conclusion: Olanzapine is a safe alternative to haloperidol in delirious critical care patients, and may be of particular interest in patients in whom haloperidol is contraindicated.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	Not a valid randomization procedure
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	randomization on an even/odd day; no further description
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	Not described
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	High	No detail (n) of exclusions
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	0	Unclear	Reporting of outcomes provided limited specific data
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: Lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Drug company sponsorship of study No ITT Baseline imbalance for age
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING =High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	0		>50 in each group
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 1**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G4-Yoon HJ, Park KM, Choi WJ, et al. Efficacy and safety of haloperidol versus atypical antipsychotic medications in the treatment of delirium. BMC Psychiatry. 2013;13:240.

Study Characteristics	Population	Study Groups	Results		Adverse Effects Comments
			Measure	Outcome	
Yoon HJ 2013 **Korea** **Setting** Tertiary level university hospital **Study Design** Prospective, comparative clinical observational study **Selection method** Patients presenting with mental status change referred to consultation psychiatric liaison service **Study Length/Start-Stop Dates** 6-days **Purpose** To compare the efficacy and safety of haloperidol versus three atypical antipsychotic medications (risperidone, olanzapine, and quetiapine) for the treatment of delirium with consideration of patient age. **Funding source(s):** Not disclosed **Quality Score** 2 **Risk of Bias**: High	**N = 146 screened** n = 130 met delirium dx criteria n = 33 with delirium excluded **N = 80 included*** **N = 53 completed trial** Dropouts -18 = discharge -6 = transfer to ICU -3 = consent withdrawn **Inclusion** Age >50 Met DSM-IV-TR criteria for delirium dx Informed consent **Exclusion** N = 33 8 = Dementia or comorbid psychiatric disorder 7 = Terminal illness 3 = Hx prolonged QTc interval 2 = Hearing loss 1 = Neuroleptic malignant syndrome 1 = Use of antipsychotic medication before referral 11 = refused to provide informed consent **Assessment** Delirium Etiology Checklist (DEC) K-MMSE (Korean version) Udvalg Kliniske Undersogelser (UKU) for side effects *NOTE: No CONSORT chart and numbers reported do not reduce to 80.	**n = 23 haloperidol group** n = 9 dropouts -5 = discharged -2 = transferred to ICU -2 = consent withdrawn Men and women (47.8%) Mean age 74.0 ± 9.9 Flexible dosing regimen: haloperidol: 0.5-10 mg,	**Delirium assessment:** DSM-IV-TR Korean version of the Delirium Rating Scale-Revised-98 (DRS-K) **Baseline characteristics** **Primary outcomes** Efficacy Mean DRS-K baseline vs Day 6 Mean K-MMSE baseline vs Day 6	All the subjects were evaluated at baseline and on the 2nd, 4th, and 6th days at the same time of day (PM 7:00–9:00). DRS-K for delirium severity. There was no significant difference between groups for demographic or clinical variables The within group effect was significant in all groups A serial decrease in the mean DRS-K severity score and increase in mean K-MMSE score was observed in all groups 17.4 (6.7) vs 7.7 (5.4) 13.7 (6.5) vs 22.4 (4.4)	**Dropouts:** No significant difference in dropouts between study groups **Safety:** No significant difference between groups Sedation = 4 (17.3%) Dystonia = 0 (0%) Rigidity = 2 (8.7%) Bradykinesia = 1 (4.3%) Tremor = 3 (13.0%) Akathisia = 1 (4.3%) Total = 5 (21.7%)
		n = 21 risperidone group n = 7 dropouts -5 = discharged -2 = transferred to ICU Men and women (61.9%) Mean age 70.1 ± 9.5 Flexible dosing regimen risperidone: 0.25-4 mg	**Delirium assessment** **Primary outcomes** Efficacy Mean DRS-K baseline vs Day 6 Mean K-MMSE baseline vs Day 6	See above 18.9 (5.2) vs 8.3 (7.1) 15.0 (5.8) vs 22.4 (5.0)	Sedation = 3 (14.2%) Dystonia = 0 (0%) Rigidity = 1 (4.7%) Bradykinesia = 1 (4.7%) Tremor = 2 (9.5%) Akathisia = 0 (0%) Total = 4 (19.0%)
		n = 18 olanzapine group n = 5 dropouts -4 = discharged -1 = transfer to ICU Men and women (55.6%) Mean age 69.5 ± 15.9 Flexible dosing regimen olanzapine: 1–20 mg	**Delirium assessment** **Primary outcomes** Efficacy Mean DRS-K baseline vs Day 6 Mean K-MMSE baseline vs Day 6	See above 17.5 (5.7) vs 8.1 (5.5) 16.2 (5.4) vs 23.1 (5.3) The response rate to olanzapine was poor in subjects > 75 yrs old compared to those <75 yrs old	Sedation = 2 (22.2%) Dystonia = 0 (0%) Rigidity = 1 (5.5%) Bradykinesia = 0 (0%) Tremor = 1 (5.5%) Akathisia = 0 (0%) Total = 4 (22.2%)
		n = 18 quetiapine group n = 6 dropouts -4 = discharged -1 = transfer to ICU -1 = consent withdrawn Men and women (55.6%) Mean age 73.3 ± 10.7 Flexible dosing regimen quetiapine: 25–200 mg	**Delirium assessment** **Primary outcomes** Efficacy Mean DRS-K baseline vs Day 6 Mean K-MMSE baseline vs Day 6	See above 17.5 (6.4) vs 6.5 (4.0) 15.7 (6.3) vs 23.4 (3.2)	Sedation = 2 (11.1%) Dystonia = 0 (0%) Rigidity = 1 (5.5%) Bradykinesia = 0 (0%) Tremor = 1 (5.5%) Akathisia = 0 (0%) Total = 2 (11.1%)
Conclusion: Although the age of subjects resulted in a different response rate for olanzapine, there was no significant difference between age groups and response rate for the other three antipsychotics. The factor of age needs to be considered in the choice of antipsychotic medication for the treatment of delirium. All of the atypical antipsychotics studied were equally effective and safe in the treatment of delirium.					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	Low	No significant differences between groups in demographic or clinical variables reported
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	Observational study
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	Observational study
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	High	Drop out = 27/80 (34%)
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Possible confounders inadequately controlled Funding source not described.
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		(assuming Korean version is validated)
8. **Sample size ≥50 each study arm (1 point if achieved)**:	0		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 2**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G4-Breitbart W, Marotta R, Platt MM, et al. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. Am J Psychiatry. 1996;153(2):231-7.

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects Comments
			Measure	Outcome	
Breitbart W 1996 **USA** **Setting** Large metropolitan Cancer Center **Study Design** RCT (double blind) **Randomization method** Hospital pharmacy conducted randomization; also identified study drug if significant adverse effects occurred **Study Length/Start-Stop Dates** 28 weeks **Purpose** To determine the safest and most effective pharmacotherapies for the management of the mental symptoms and behavioral disturbances associated with delirium in AIDs patients. **Funding source(s):** Not described **Quality Score** 3 **Risk of Bias**: Unclear	**N = 419 approached for participation** **N = 244 informed consent** **N = 30 developed delirium** Men and women (23%) Mean age 39.2 (8.8) (23-56) **Inclusion** AIDS-related medical problems Medically stable Informed consent (to delirium protocol if delirium developed) Delirium present during study period **Exclusion** N = 175 (no specific data) Hypersensitivity to neuroleptics Hypersensitivity to benzodiazepines Presence of neuroleptic malignant syndrome Concurrent treatment with neuroleptic drugs Seizure disorder Current systemic chemo-therapy Withdrawal syndrome Anticholinergic delirium Current or past dx -schizophrenia -schizoaffective disorder -bipolar disorder Participation would compromise obtaining needed medical treatment Delirium associated with terminal event Lacked capacity for informed consent **Assessments** Delirium Rating Scale (DRS) DSM III R MMSE (also used to guide ratings on delirium severity) Extrapyramidal Symptom Rating Scale (ESRS) Side Effects and Symptoms Checklist Mental Status Profile	**n = 11 haloperidol** Treatment group-specific demographics not described Treatment protocol established for each study drug. Dose level mg (1-9) for oral and intramuscular administration Table 1, p 233 in PDF	**Delirium assessment:** DSM III R Delirium Rating Scale MMSE **Baseline characteristics** **Primary outcomes** Mean dose first 24 h (mg) Average maintenance dose Average DRS baseline Average DRS day 2 Average DRS end of tx Main effect for time Significant decrease in DRS Baseline to day 2 No significant difference in DRS day 2 to end of tx	Trained research staff monitored study patients daily for signs of delirium. Medical and nursing staff also trained. If delirium was suspected the study coordinator and study psychiatrist performed a full assessment Each study drug treatment protocol initiated (blinded); patients evaluated hourly with DRS, MMSE and ESRS No significant difference between treatment groups **Haloperidol vs chlorpromazine vs lorazepam** 2.8 (2.4) vs50 (23.1) vs 3.0 (3,.6) 1.4 (1.2) vs 36.0 (18.4) vs 4.6 (4.7) 20.45 (3.45) vs 20.62 (3.88) vs 18.33 (2.58) 12.45 (5.87) vs 12.08 (6.50) vs 17.33 (4,18) 11.64 (6.10) vs 11.85 (6.74) vs 17.00 (4.98) F = 10.09, df=2,27, p<0.001 Main effect for drug NS (p<0.44) F = 27.50, df=1, 27, p<0.001 P<0.43 vs p<0.81 vs p<0.81	No significant difference -medical complications p<0.32 -severity of complications p<0.61 Deaths (within 8 days of protocol initiation) n = 2 haloperidol n = 2 chlorpromazine n = 1 lorazepam Deaths within 1 week after completing the protocol n = 3 chlorpromazine n = 1 lorazepam Extrapyramidal side effects = none -no effect for time, p<0.81 -drug by time interaction = trend, p<0.07 -increase in lorazepam group **Comments** This study confirmed the clinical efficacy of neuroleptic drugs in the amelioration of delirium symptoms in AIDS patients. In addition, lorazepam alone is not effective in the treatment of delirium in AIDS patients, The doses of neuroleptics required to manage delirium in AIDS patients may be considerably lower than many reported in clinical standards. There may be disease specific mechanisms that explain why patients with AIDS required low doses.
		n = 13 chlorpromazine Treatment protocol – see above Table 1, p 233 in PDF	**Delirium assessment:** **Primary outcomes** Significant decrease in DRS Baseline to day 2 MMSE baseline to day 2 MMSE baseline to end of tx	See above F=37.02, df=1, 27, p<0.001 MMSE improved only for chlorpromazine group F=13.99, df=1,27, p<0.001 F=4.68, df=1,27, p<0.04	
		n = 6 lorazepam Treatment protocol – see above Table 1, p 233 in PDF	**Delirium assessment** **Primary outcomes** No significant decrease in DRS Baseline to day 2 Treatment-limiting side effects	See above F=0.23, df=1,27, p<0.63 All 6 patients developed side effects -increased confusion -oversedation -disinhibition -ataxia Lorazepam treatment discontinued Subsequent patients randomized to haloperidol or chlorpromazine	

Conclusion: Symptoms of delirium in medically hospitalized AIDS patients may be treated efficaciously with few side effects by using low-dose neuroleptics (haloperidol or chlorpromazine). Lorazepam alone appears to be ineffective and associated with treatment-limiting adverse effects.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	Unclear	Baseline date not reported except for age and gender of 30 patients with delirium
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	Unclear	Not clear whether outcome assessors were blinded
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	Unclear	Total patients approached and number consented, but no specific data on exclusions
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	All patients analyzed, but ITT protocol not performed Funding not disclosed
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = Unclear**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	0		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 3**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G1-Sieber FE, Zakriya KJ, Gottschlack A, et. al., Sedation Depth During Spinal Anesthesia and the Development of Postoperative Delirium in Elderly Patients Undergoing Hip Fracture Repair, Mayo Clinic Proc. 2010; 85(1):18-26.

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects Comments
			Measure	**Outcome**	
Sieber F 2010 **USA** **Setting** Johns Hopkins Bayview Medical Center **Study Design** RCT – parallel groups **Randomization method** Patients were randomized to receive deep or light sedation using a randomized block design with random length blocks. Randomization incorporated a stratification scheme for age (>80 years or 65-80 years) and cognitive impairment (MMSE score, 24-30 or 15-23). Blinding of all study team members except attending anesthesiologist **Study Length/Start-Stop Dates** 4/2/2005-10/30/2008 **Purpose** To determine whether limiting intraoperative sedation depth during spinal anesthesia for hip fracture repair in elderly patients can decrease the prevalence of postoperative delirium. **Funding source(s):** Grant K08AG029157/AG/NIA NIH HHS **Quality Score** 8 **Risk of Bias**: Low	N= 457 hip fracture patients screened n = 54 not eligible n = 289 not randomized N= 114 Randomized n = 57 Deep sedation n= 57 Light sedation n = 0 withdrew **Inclusion** -Age ≥65 yrs -Hip Fracture repair surgery -Spinal anesthesia -Propofol sedation -Informed consent **Exclusion** -N=170 - n=10, Refusal of spinal anes - n=4, Language barriers - n=42, Pre-op cognitive impairment (MMSE score <15) - n=37, Pre-op delirium (+CAM score) - n=61, pre-op dementia and delirium -n=16, Contraindications to spinal anesthesia e.g.: Aortic stenosis Coagulopathy Anticoagulants use Spinal cord disease - Prior hip surgery - Mental barriers - Severe congestive heart failure - Severe COPD **Protocols (all patients)** **Pre-op screening** MMSE CAM **Standardized :** -Intra-op monitoring -Anesthesia administration (≤2mg midazolam, 11.25 mg 0.75% bupivacaine) -Post-op analgesics	**n = 57 Deep sedation group** n = 4 converted to general anesthesia Men and women (75.4%) Mean age = 81.8±6.7 MMSE score, mean 24.5±5.3 Pre-op MMSE <24 = 21 (37) Depression = 14 (25) Benzodiazepine use = 2 (4) Antidepressant use =10 (18) Opioid use = 4 (7) **Intervention** Bispectral index (BIS) monitoring targeted to approximately 50	**Delirium assessment:** CAM **Baseline characteristics** **Intra-operative Data** Duration of Surgery (min) Propofol dose (mg/kg) Receiving midazolam Midazolam dose Average BIS, mean (SD) Range 0-100 Average BIS <50, mean (SD) **Primary outcomes** Postoperative delirium **Significant secondary outcomes** Duration of delirium, (all patients) mean (SD) d Delirium in patients with: pre-op MMSE(score ≥20) pre-op MMSE(score ≥24)	Trained research nurse performed daily CAM from 2nd day post-op. until discharge at approx. 10am **Deep (57) v Light (57) Sedation** No significant differences *Significant differences* 93 (44) v 79 (33) , p=0.05 10.2 (5.6) v 2.5 (2.7), p<.001 3(5) v 11 (19) , p=.04 1.26 (6.36) v 5.53 (12.42), p=.02 49.9 (13.5) v 85.7 (11.3), p <.001 48 (34) v 4 (18), p <.001 23 (40) v 11 (19), p=.02 1.4 (4.0) v 0.5 (1.5), p=.01 14(44) v 5(14), p=.01 11(39) v 3(11), p=.03	**Adverse Effects** None reported **Comments:** One limitation of the current study is the exclusion of patients with MMSE scores of less than 15, restricting the generalizability of the results to patients with at most moderate dementia. Dementia assessment in this study might have been more reliable using a clinical consensus, rather than primary care physician diagnosis and the MMSE. All data analyzed on ITT basis
		n = 57 light sedation group n = 6 converted to general anesthesia Men and women (70.1%) Mean age = 81.2±7.6 MMSE score, mean = 24.8±4.6 Pre-op MMSE <24 = 19 (33) Depression = 11 (19) Benzodiazepine = 3 (5) Antidepressant use = 9 (16) Opioid use = 2 (4) **Intervention** BIS monitoring target to approximately 80 (or higher)	**Delirium assessment:** **Baseline characteristic** **Primary outcomes** **Secondary outcomes** **Significant Predictors of Post-operative Delirium** (univariate analysis) Deep vs light sedation Average BIS Duration BIS <50 Preoperative dementia Preop MMSE score Preoperative ADL Units of packed erythrocytes transfused ≥1 Postop complications No. of post-op complications Admission to ICU without prior delirium Length of ICU stay	See above See above See above See above **OR (CI), p** 2.83 (1.20-6.62), p = .01 0.97 (0.954-0.995), p=.01 1.001 (1.00-1.023), p=.05 3.56 (1.52-8.32), p=.003 0.86 (0.78-0.95), p=.001 0.72 (0.54-0.98), p=.02 1.58 (1.12-2.22), p=.007 2.48 (1,.07-5.75), p=.03 1.50 (1.08 -2.09), p=.02 8.19 (1.44-46.4), p=.02 1.28 (1,.02-1.59), p=.02	

Conclusion: The use of light propofol sedation decreased the prevalence of postoperative delirium by 50% compared with deep sedation. Limiting depth of sedation during spinal anesthesia is a simple, safe, and cost-effective intervention for preventing postoperative delirium in elderly patients that could be widely and readily adopted.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	1	Low	
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	1	Low	
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = Low**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		CAM
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 8**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G1- Santarpino G, Fasol R, Sirch J, et. al. Impact of bispectral index monitoring on postoperative delirium in patients undergoing aortic surgery, HSR Proc Intensive Care Cardiovasc Anesth. 2011; 3(1): 47-58.

Study Characteristics	Population	Results						
		Measure	**Group I n=52** **BIS Reduc** ≤15%	**Group II n=125** **BIS Reduc** 15-20%	**Group III n= 68** **BIS Reduc** 20-25%	**Group IV n=33** **BIS Reduc** 25-30%	**Group V n=14** **BIS Reduc** >30%	**Significant difference between groups**
Santarpino G 2011 Deutschland **Setting** Inpatients (Clinical and hospital records) **Study Design** Observational - Retrospective analysis **Selection method** Consecutive patients fitting inclusion criteria **Study Length/Start-Stop Dates** 12/2006-12/2009 **Purpose** To evaluate the role of Bispectral index (BIS) in ostoperative neurological outcome of patients undergoing aortic surgery, with special reference to motor function and delirium. **Funding source(s):** Not disclosed **Quality Score** 3 **Risk of Bias**: High	**N = 292** n = 53 BIS reduction ≤15% n = 125 BIS reduc 15-20% n = 68 BIS reduc 20-25% n = 33 BIS reduc 25-30% n = 14 BIS reduc >30% **Inclusion** - Age ≥18 - Aortic surgery - Replacement of ascending aorta combined with -aortic arch, -valve replacement or -coronary artery bypass **Exclusions** Clinical instrumental findings showing postop -low cardiac output -acute renal or liver failure Not entered in database as associated with postop delirium and not analyzed **Protocol Standardized:** -Anesthetic technique - Cardiopulmonary bypass (CPB) -Surgical technique -Post-op care **BIS Reduction Calculation** Baseline BIS value and the minimum BIS value recorded during surgery was determined (baseline value-minimum value/baseline value x 100). Time interval was arbitrarily set to >15 min to minimize the rate of false positives	**Delirium assessment:** DSM-IV Differential dx performed by anesthesia staff in the ICU.						**Preoperative (Baseline)** **Significant differences for dissections** (v elective) - Age (older p<0.001) - Hypertension (more p<0.001) - Hypercholesterolemia (more p = 0.017) - Intubation times (p<0.001) - CPB times (p<0.001) - Cross-clamping times (p <0.001) - Length of ICU stay(p <0.001) - Body temperature (p <0.001) **Cumulative difference in:** -Delirium, p<0.001 -Neurological events, p<0.001 -Length of ICU stay, p=0.003 -Intubation time, p=0.001 **Post hoc analysis:** - Only Group V showed a longer ICU stay compared to -Group I (p=0.002), -Group II (p=0.005) -Group III (p=0.015). - Group V also showed a longer intubation time compared to -Group I (p=0.008) -Group II (p=0.002). - Length of ICU stay -Group I vs V (p=0.013) - Group II vs V (p=0.023) - Intubation time -Group II vs V (p=0.01). - Incidence of neurological events -higher in Group V (p<0.001) - Incidence of delirium -Group IV (p<0.001) **Aortic dissections vs elective surgery** **Aortic dissection** -All deaths (n=19, p<0.001). - Higher incidence of post-op neurological events (p=0.01) - Higher incidence of delirium (p=0.007) -Higher incidence of delirium requiring therapy (p=0.03).
		Baseline characteristics						
		Age (years)	59.7±15	60.0±14.3	60.2±11.9	53.6±11.2	58.7±10.9	
		EuroSCORE	10.3±3.2	10.2±3.6	9.9±2.8	10.7±3.5	10.1±3.2	
		Height (cm)	172.1±9.2	172.7±9.5	171.9±10.2	177.8±10.8	174.9±8.4	
		Weight(kg)	80.4±13.9	81.4±16.7	84.6±25.2	84.6±14.5	81.4±14.4	
		NYHA class	1.2±1.4	1.3±1.5	1.0±1.3	0.7±1.3	1.1±1.3	
		LVEF (%)	63.5±11.7	59.2±12.8	60.7±10.2	58.4±10.9	61.3±8	
		Procedure time (min)	272±126	285.7±115.9	268.0±117.0	287±113.2	331±117.7	
		CPB time (min)	165.2±94.1	165.8±76.2	162.2±83.2	171.6±70.1	205.4±89.7	
		Cross-clamping time (min)	95.7±50.5	88.4±36.8	93.4±43.4	101.5±44.6	108.2±50	
		Minimum temp (C)	28.7±6.0	28.5±5.4	29.1±5.6	26.8±6.5	26.5±6.6	
		Type of surgery						
		Ascending aorta + CABG	0	2(1.6%)	1(3%)	1 (3%)	0	
		Ascending aorta + AVR	32(61%)	72(57.6%)	22(66.7%)	22(66.7%)	6(43%)	
		Ascending aorta – AVR	16(31%)	42(33.6%)	8(24.2%)	8(24.2%)	4(29%)	
		with arch	4(7.7%)	9(7.2%)	2(6.1%)	2(6.1%)	4(29%)	
		Primary outcomes						
		Incidence of delirium (N = 53)	3(5.8%)	5(4%)	5(7.4%)	30(90.9%)	10(71%)	
		Delirium requiring therapy	2(3.8%)	4(3.2%	1(1.5%)	15(45.5%)	9(64%)	
		Neurological complications (N = 29)						
		TIA	0	0	0	0	1(7.1%)	
		RIND	0	2(1.6%)	1(1.5%)	0	0	
		Stroke	3(5.8%)	4(3.2%)	1(1.5%)	6(18.2%)	11(79%)	
		Secondary outcomes						
		Mortality	3(5.8%)	9(7.2%)	4(5.9%)	1(3%)	2(14%)	
		Intubation time	73.3±112	105.2±177.8	106.6±209.4	133.5±169	228.2±211.3	
		ICU length of stay	5.4±6.6	7.3±8.6	6.7±6.5	8.7±8.3	13.5±10.3	

Conclusion: Intraoperative cerebral monitoring with BIS can predict postoperative delirium when a BIS reduction of 25-30% is observed. Several confounding factors likely affected the reported BIS values, but if these findings are confirmed by additional research, they would translate to improved quality of care, Explanations of these findings are speculative with regard to the underlying mechanisms and larger studies are warranted to clarify these issues.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jaded scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	NA – Observational study , but with Baseline differences between groups
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	NA - Observational Study
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	NA -Observational Study
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	(Excluded data described)
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	0	Unclear	Author notes variables known to affect postop delirium risk not included
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Funding not disclosed. Study limitations: -BIS group classifications arbitrary -Time interval not supported by the literature -Retrospective design -Clinical records did not record BIS measuring device -Variables known to affect postop risk not included
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		N = 292 (no intervention groups)
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 3**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

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  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G1-Chan MT, Cheng BC, Lee TM, et al. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. J Neurosurg Anesthesiol. 2013;25(1):33-42.

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects
			Measure	Outcome	
Chan 2013 **China** **Setting** University Hospital **Study Design** RCT – Double blind Cognitive Dysfunction After Anesthesia (CODA Trial) **Randomization method** computer-generated random group assignment **Study Length/Start-Stop Dates** 1/2007 to 12/ 2009 **Purpose** To determine whether bispectral index (BIS)-guided anesthesia decreases the incidence of post operative cognitive dysfunction (POCD) and postoperative delirium in elderly patients undergoing major surgery. **Funding source(s):** Competitive Earmarked Research Grant (CUHK4400/ 06M), Research Grants Council of Hong Kong, and Health and Health Services Research Fund (04060271). **Quality Score** 6 **Risk of Bias**: High	**N = 1657 screened** n = 736 excluded (see below) **N = 921 randomized** n = 462 BIS guided n = 80 excluded 8-surgery canceled 4 regional only 6 died before test 7 refused testing 55 unfit for testing n = 459 routine care n = 58 excluded 4 surgery canceled 3 regional only 4 died before test 5 refused testing 42 unfit for testing **Inclusion** Age >60 yrs Elective major surgery Duration >2 hrs Hospital stay of >4 days **Exclusion** N = 736 660 Other research 62 MMSE≤ 23 10 refused 4 No reason stated **Assessments** 1 week before surgery 1 week after surgery 3 months after surgery MMSE Cognitive failure questionnaire questionnaire (CFQ) Verbal fluency test Chinese auditory verbal learning test Color trial Quality of recovery (QoR) 3 months postop Short-Form Health Survey (SF-36)	**n = 450 BIS guided anesthesia group** (baseline and Men and women (37.8%) Mean age 68.1±8.2 BIS group had anesthesia adjusted to maintain a BIS value between 40 and 60 during maintenance of anesthesia.	**Delirium assessment:** CAM **Baseline characteristics** **Primary outcomes** POCD at 3 months postop Absolute risk reduction NNT **Secondary outcomes** Incidence of delirium in hospital QoR Day 1 QoR Hospital discharge ***Significant Risk Factors of Postoperative Delirium*** Intraoperative BIS value Time with BIS<40 h End-tidal volatile concentration ***Significant Risk Factors of Cognitive Dysfunction at 3 mon*** Age + POCD Delirium Intraop BIS value Time with BIS <40 (h) End-tidal volatile concentration (MAC equivalents)	Delirium was assessed daily in the mornings after surgery using CAM criteria based on cog testing (MMSE, neuro-psych tests). Inter-rater reliability was not discussed. CAM and MMSE administered at 1 week and 3 month follow up. Delirium severity was not discussed. No significant difference between groups **BIS vs routine care** 42/412 (10.2%) vs 62/423 (14.7%), p=0.02 4.5% (0.25-8.9) 23 (6-391) **BIS vs routine care** 70/450 (15.6%) vs 109/452, p= 0.01 11.8±2.1 vs 9.8±2.4 p<0.001 16.3±1.7 vs 15.3±2.1 p<0.001 **N = 902 OR (CI), p** Multivariable analysuis 0.91 (0.87-0.96) P<0.001 2.05 (1.02-4.16) P=0.03 1.15 (1.05-7.34) P<0.04 **N = 835 OR (CI), p** Multivariable Analysis 1.04 (1.01-1.08), p=0.01 9.58 (4.62-19.9), p<0.001 0.93 (0.85-0.97) p<0.001 1.11 (1.01-1.96) p=0.04 2.31 (1.15-15.6) p=0.03	**Postop complications** **BIS vs routine** *Cardiac*: 28 (6.2) vs 33 (7.3) p=0.13 *Respiratory* 64 (14.2) vs 81 (17.9) p=0.67 *Infection* 75 (16.7) vs 104 (23.0) p=0.02 *Any complication* 48 (10.7) vs 94 (20.8) p=0.01 **Comments:** The CODA Trial indicated that for every 1000 patients undergoing major surgery, BIS-guided anesthesia prevented 83 patients from suffering delirium during hospital admission and 23 patients from POCD at 3 months after surgery. Given that intraoperative low BIS value, long period of deep anesthesia (BIS<40), and large doses of anesthetic were predictors of POCD, BIS monitoring with careful titration of anesthetics should prevent unintentional deep anesthesia and may be useful for improving postoperative cognitive performance in the elderly.
		n = 452 routine care group Men and women (39.6%) Mean age 67.6±8.3 Routine care group had BIS measured but not revealed to attending anesthesiologists. Anesthesia was adjusted according to traditional clinical signs and hemodynamic parameters.	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Secondary outcomes**	See above	
Conclusion: BIS-guided anesthesia reduced anesthetic exposure and decreased the risk of POCD at 3 months after surgery. For every 1000 elderly patients undergoing major surgery, anesthetic delivery titrated to a range of BIS between 40 and 60 would prevent 23 patients from POCD and 83 patients from delirium.					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	1	Low	
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	High	Drop out >10%
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	No ITT analysis Very large % of exclusions after randomization and dropouts at 3 month primary outcome analysis
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 6**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
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  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G1-Radtke FM, Franck M, Lendner J, et. al., Monitoring depth of anesthesia in a randomized trial decreases the rate of postoperative delirium but not the postoperative cognitive dysfunction, Br J Anaesth. 2013; 110 Suppl1:i98-105.

Study Characteristics	Population	Intervention Groups	Results: Measure	Results: Outcome	Exclusions Comments
Radtke F 2013 **Germany** **Setting** University hospital **Study Design** RCT- Parallel groups **Randomization method** Stratification Consecutive patient sample randomized according to ASA PS (I/II vs III/IV) and electronically randomized into two study groups **Study Length/Start-Stop Dates** 3/2009-5/2010 Follow-up until 8/2010 **Purpose** To assess whether bispectral index (BIS) guided anesthesia versus routine care reduces the incidence of postoperative delirium in elderly patients.. **Funding source(s):** supported by Charite´-Universita¨tsmedizin Berlin with additional funding provided by Aspect Medical Systems, now Covidien **Quality Score** 4 **Risk of Bias**: High	**N = 1277 randomized** n = 638 BIS guided *n = 45 did not receive BIS guided* n= 639 BIS blinded *n = 39 did not receive BIS blinded intervention* **N = 1155 analyzed** n= 575 BIS guided n= 580 BIS blinded **Inclusion** - Age ≥60 yr - Elective surgery ≥60 min -General -Abdominal -Thoracic - Vascular - Orthopedic -Otorhinolaryngological -Oral & maxillofacial -Gynecological - Urologic al -Informed consent **Exclusion** - MMSE score <24 - Hx Neurologic defects -Stroke -Seizures, etc -Pharmaceutical study participation -Not planned for general anesthesia -Language barrier **Protocol** All patients received pre-, peri- and post-op treatment, as specified in the standard operating procedures (SOPs) of the hospital.	**n= 575 BIS guided anesthesia** Mean age = 69.7 (6.3) Men and Women (44.7%) ASA PS I and II = 305 (53.0%) III and IV = 270 (47.0%) Surgical specialty: General surgery = 275 (47.8%) Orthopedics = 182 (31.7%) Urology = 40 (7.0%) Gynecology = 64 (11.1%) Other = 14 (2.4%) MMSE (mean) = 28.8 (1.5) **Intervention** Anesthesiologists were allowed to use the bispectral index (BIS) data to guide anesthesia **Blinding**: OR coordinator not blinded and scheduled patients according to allocation: -BIS guided anesthesiologists always used BIS monitoring -BIS blinded anesthesiologists never used BIS monitoring Both anesthesiologist groups' qualifications were broadly comparable in order to avoid a possible "investigator bias" -a switch between teams was excluded	**Delirium assessment:** DSM IV POCD **Baseline characteristics** **Primary outcomes** Postoperative delirium incidence Postoperative delirium, n %; CI, p N avg BIS values <20 Duration of surgery ***Multivariate analysis*** Age Duration of surgery MMSE % BIS <20 **Multivariate analysis of mortality** Duration of surgery Delirium ASA PS	**Delirium assessed** 2 x day from POD1 to POD 7 by trained medical personnel supervised by a psychiatrist and delirium experts, all were blinded to tx group. **Postop cognitive dysfunction (POCD)** assessed the evening before surgery and 7 days and 3 months after surgery: - Motor screening test - Pattern recognition - Spatial recognition -Attention (choice reaction time) No significant differences between groups patients who received interventions N = 191 (18.8%) **BIS guided (575) v BIS blinded (580)** 95 (16.7%;13.9 to 20%) v 124 (21.4%); 18.3 to 24.9%), p = 0.036 3.7 (10.8) v 5.6 (19.5), p = 0.040 164 (98) v 175 (105) p = 0.055 ***Significant differences Delirium v no delirium*** 1.096 (1.065 to 1.127), p <0.001 1.008 (1.006 to 1.009), p <0.001 0.832 (0.749 to 0.925) p = 0.001 1.027 (1.008 to 1.046) p = 0.006 **Significant predictors at 3 months postop** 1.003 (1.001 to 1.006), p = 0.005 2.048 (1.15 to 3.65) p = 0.015 1.947 (1.124 to 3.371) p = 0.017	**n= 45 did not receive assigned BIS-guided anesthesia** n=19 missed canceled surgery n=6 inclusion criteria n=3 withdrawal of consent n= 2 technical difficulties n=4 regional anesthesia n= 2 in prone position n= 1 hospital staff n= 8 unknown reason n= 18 lost to follow-up **n = 18 lost to follow up** n = 11 discharged or transferred early n = 7 unknown reason **Comments** **POCD:** There was increased tendency in the BIS blinded group (p=0.062), but no correlation for POCD on the 19th POD
		n=580 BIS blinded anesthesia Mean age = 70.1 (6.5) Men and Women (47.6%) ASA PS I and II = 300 (51.7%) III and IV = 280 (48.3%) Surgical specialty: General surgery = 284 (49.0%) Orthopedics = 153 (26.4%) Urology = 63 (10.9%) Gynecology = 61 (10.5%) Other = 19 (3.3%) MMSE (mean) = 28.9 (1.5) **Intervention** BIS monitoring was blinded	**Delirium assessment:** **Baseline characteristics** **Primary outcomes**	See above See above See above	**n= 39 did not receive assigned BIS-blinded anesthesia** n= 14 missed canceled surgery n= 8 inclusion criteria n= 5 withdrawal of consent n= 5 technical difficulties n= 1 regional anesthesia n=1 died n=5 unknown reason n=20 lost to follow-up **n = 20 lost to follow up** n = 9 discharged or transferred early n = 1 refused n = 10 unknown reason

Conclusion: Intraoperative neuromonitoring may change anesthetic management and is correlated with a lower incidence of delirium, possibly by reducing extreme low BIS values. In high risk surgical patients this may give the anesthesiologist at hand a possibility to influence one precipitating factor in the complex genesis of delirium.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	Unclear	Unclear due to large % of originally randomized patients who did not receive treatment or were lost to follow up in both groups. Had they been included in analysis there may have been a significant difference in baseline characteristics
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	Unclear	The OR coordinator was not blinded; but it is not clear whether this affected other participants knowledge of allocation
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	1	Low	All others were reported as blinded
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	High	>10% exclusion + lost to follow up (those who did not receive the assigned treatment after randomization)
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Funded partly by Aspect Medical Systems (now Covidien)
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 4**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G2 Larsen KA, Kelly SE, Stern TA, Bode RH, Jr., et al. Administration of olanzapine to prevent postoperative delirium in elderly joint-replacement patients: a randomized, controlled trial. Psychosomatics. 2010;51(5):409-418.

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects
			Measure	Outcome	
Larsen 2010 **USA** **Setting** Single center Inpatient **Study Design** RCT – double blind, placebo controlled **Randomization method** – initially stratified into two cohorts simple vs complex; randomly assigned by computer random-number table to intervention or placebo; all patients and personnel blinded throughout the trial **Study Length/Start-Stop Dates** Recruitment 2005 to 2007 **Purpose** To evaluate the impact of the peri-operative administration of olanzapine on the prevention of postoperative in elderly patients undergoing elective joint replacement surgery. **Funding source(s):** Grant from hospital and Eli Lily provided drugs **Quality Score: 5** **Risk of Bias**: **High**	**N = 495** n = 246 intervention n = 252 placebo **Dropouts** (detail in AE) N = 95 n = 50 intervention n = 48 placebo . **Inclusion** Age ≥ 65 Age <65 with postop delirium hx Elective total knee or hip replacement English speaking Able to provide informed consent **Exclusion** N = not specified Dx dementia (<1% of study population) Alcohol use ≥10 alcohol drinks/week Hx alcohol dependence or abuse Allergy to olanzapine Current use of antipsychotic medication **Preadmission screening** ASA classification based on medical comorbidities **Preoperative procedures** Nurses not involved with postop care administered 5 mg olanzapine or placebo immediately before surgery **Operative procedures** Anesthesia protocols were consistent for all patients **Postoperative procedures** Nurses not involved with the study administered second dose (5.mg) of olanzapine or placebo Routine postop analgesics administered with transfer to nursing floor after 4-6 h **Delirium Dx** Determined by blinded reviewer	**Simple hip/knee replacement** **n = 207 10 mg olanzapine** **Complex hip/knee replacement** **n = 36 10 mg olanzapine** Men and women (48.0%) Mean age 73.4 (6.1) ASA 3 = 39.5% After transfer to nursing floor -Research asst (RA) interviewed patients and obtained info from nursing staff -mental status (MMSE) -signs/sx of delirium -nurses (Confusion Assessment Method – CAM) -RA administered Delirium Rating Scale-Revised-98 (DRS-R-98) -blinded clinical psychologist verified daily data -daily assessments post op days 1-8 (or discharge)	**Delirium assessment:** DSM-III-R criteria MMSE DRS-R-98 CAM **Provide baseline characteristics/measures** Sex **Primary outcomes** Delirium Delirium in knee surgery Delirium in hip surgery Delirium in simple surgery Delirium in complex surgery Time to onset of delirium Duration of delirium Severity of delirium (DRS-R-98) **Secondary outcomes** *Significant differences only* Home with services) Rehab facility Abnormal labs Use of restraints NNT	RAs did daily MMSE and DRS days 1-8; Co-investigator determined if DSM IIIR criteria met No significant difference for demographics and surgical characteristics, except Fewer women (48%) **N = 196** Olanzapine vs placebo 14.3% vs 40.2% (17.6 to 34.2), p <0.0001 17.7 vs 47.8% (18.8 to 41.4) p <0.0001 7,6% vs 30.8% (11.8 to 34.6, p=0.0004 12.4% vs 40.9% (18.8 to 37.5), p <0.0001 25.9% vs 37.5% (10.7 to 33.99), p =0.32 p <0.0001 (see Figure 3) 2.2 d (SD 1.3) vs 1.6 d (SD 0.7), p=0.02 16.44 (SD 3.7) vs14,5 (SD 2,.7), p=0.02 Olanzapine vs placebo 41% vs 30% p, 0.02 59% vs 70% (p not reported) 53.6% vs 19.5% p <0.0005 2.6% vs 0%, p=003 4 (Lower incidence of delirium 14.4% vs 40.2%)	*No serious adverse effects reported but large n overall* (156, 79%) Simple cohort **dropouts** before surgery -Anxiety (22) -Surgery cancelled (7) -Family pressure (2) -Drug not given (3) -Medical advice (2) -Clerical error (2) Complex cohort **dropouts** before surgery -Anxiety (3) -Surgery cancelled (1) -Family pressure (3) -Medical advice (1) -Clerical error (1) **Independent risk factors for post-operative delirium** -Advanced age -Knee replacement surgery -abnormal albumin level -High ASA score
		Simple hip/knee replacement **n = 209 placebo** **Complex hip/knee replacement** **n = 43 placebo** Men and women (60.3%) Mean age 74.0 (6.2) ASA 3 = 45.3%	**Delirium assessment:** **Provide baseline characteristics/measures** Sex **Primary outcomes** Delirium **Secondary outcomes**	Same as above No significant difference for demographics and surgical characteristics, except More women (60.3%) **N = 204** See above See above	*No serious adverse effects reported but large n overall* (156, 59%) Simple cohort **dropouts** before surgery -Anxiety (16) -Surgery cancelled (12) -Family pressure (12) -Drug not given (3) -Medical advice (2) Complex cohort **dropouts** before surgery -Anxiety (1) -Surgery cancelled (1) -Family pressure (1)
Comments: No ITT analysis. Preoperative misrepresentation in 5 (17.9%) patients who developed delirium in the olanzapine-treated group and 1 (1.2%), may have resulted in alcohol withdrawal in the patients analyzed in this study. The high incidence of abnormally low albumin levels occurred in the olanzapine-treated patients. Olanzapine treated patients also used less narcotic medication suggesting it may have reduced the need for analgesics .					
Conclusion: Administration of 10 mg of oral olanzapine perioperative vs placebo was associated with a significantly lower incidence of delirium. Olanzapine reduced the incidence of delirium, but not its severity or duration. These findings suggest that olanzapine prophylaxis of postoperative delirium may be an effective strategy. .					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	1	Low	
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	High	Detail on exclusions not reported Large number of post-randomization dropouts
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	0	Unclear	Some secondary outcomes were not reported (perceived pain; narcotic use (specific), hypotension, LOS); Large number of AEs in olanzapine group (156, 79%) vs placebo (156, 59%)
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	No ITT analysis Data reporting discrepancies Eli Lily provided drug 1 of first authors funded by Eli Lily
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 5**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

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  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G2-van den Boogaard M, Schoonhoven L, van Achterberg T, et al. Haloperidol prophylaxis in critically ill patients with a high risk for delirium. Crit Care. 2013;17(1):R9.

Study Characteristics	Population	Study Groups	Results		Adverse Effects
			Measure	Outcome	
van den Boogaard M 2013 **Netherlands** **Setting** ICU of a university tertiary care hospital **Study Design** Before/After Observational study **Selection method** All consecutive patients: 2008 – 2009 as a control period, 2010 -2011 as a intervention period **Study Length/Start-Stop Dates** 2/2008 to 2/2009 8/2010 to 8/2011 **Purpose** To evaluate the ICU delirium prevention policy/protocol resulted in quality improvement of relevant delirium outcome measures. PREdiction DELIRium Intensive Care score (PREDELIRIC). **Funding source(s):** Not described; authors reported no conflicts of interest **Quality Score** 4 **Risk of Bias**: High	**N = 476 allocated to intervention / control** n = 177 intervention n = 299 control **Intervention group** N = 2320 n = 2084 excluded -low delirium risk -delirium <1 day -sustained coma n = non treated patients -20 non-compliance -22 prevention started too late -5 PREDELIRIC score known too late -11 haloperidol contraindicated -2 inclusion missed (alcohol abuse) Age >18 yr PREDELIRIC >50% history of dementia or alcohol abuse Haloperidol dosage adjusted or stopped **Control group** N = 2132 n = 1833 excluded -low risk -delirium <1 day -sustained coma **Other exclusion criteria** Not possible to assess patient Serious auditory or visual disorders Inability to understand Dutch Severe mental disability Presence of receptive aphasia	**n = 177 Haloperidol prevention group** Men and women (35%) Mean age 63 ± 14 Consecutive patients screened for delirium risk -PREDELIRIC score >50% -dementia dx -alcohol abuse in medical hx ICU patients with a high risk for delirium who are treated with haloperidol for preventive reason. These high-risk patients received intravenous haloperidol 1 mg/8 h or -a lower dose of 0.5 mg/8 h ⩾ 80 years body weight <50 kg, serum creatinine level >150 µmol/L serum bilirubin level >50 µmol/L. Intravenous haloperidol prophylaxis was started as soon as it was clear that patients had an increased risk, ranging from immediately following ICU admission to 24 hours after ICU admission.	**Delirium assessment:** CAM-ICU (Dutch version) RASS PREDELIRIC score **Baseline characteristics** APACHE-II score Admitted with sepsis Sedation level (RASS) - RASS screening compliance Haloperidol administering - Number of treated patients - Number of treated days PRE-DELIRIC score Alcohol abuse Dementia **Primary outcomes** CAM ICU screening compliance Delirium incidence Number of delirium free days without coma in 28 days 28-day mortality **Secondary outcomes** hrs on the ventilator length of stay on the ICU length of stay in-Hospital incidence of re-intubation incidence of re-admissions Unplanned removal tubes/lines Delirium subtype: - Hyperactive - Hypoactive - Mixed	Trained ICU nurses performed Dutch version of the CAM-ICU at least 3 times daily. inter-rater reliability was high **Control vs Intervention** 20 ± 7 vs 19 ± 6, p=0.06 64 (21%) vs 53 (30%), **p= 0.02** -1 (-3 to 0) vs -1 (-3 to 0) 93.3% ± 1.2 vs 94.5% ± 0.9 225 (75.3%) vs 177 (100%), **p <0.0001** 5 (2 to 12) vs 5 (3 to 11), p=.23 73 ± 22 vs 75 ± 19, p= 0.50 41 (14%) vs 20 (11%) p=0.37 5 (2%) vs 2 (1%) **Control vs Intervention** 90.4% vs 94.5% 225 (75%) vs 115 (65%), p=.01 13 (3 to 27) vs 20 (8 to 27), p = 0.003 36 (12%) vs 13 (7.3%), p=0.03 118 (39 to 250) vs 90 (36 to 229) , p= 0.24 7 (3 to 13) vs 6 (3 to 12), p=.65 21 (12 to 41) vs 20 (11 to 31), p= 0.16 25 (8%) vs15 (9%), p= 0.51 55 (18%) vs 20 (11%), p= 0.03 58 (19%) vs 21 (12%), p= 0.02 20 (7%) vs 6 (3%) 81 (27%) vs 33 (19%) 124 (41%) vs 76 (43%)	**In haloperidol treatment group** 14/177 (8%) adjusted dosage (6%) drowsiness 12 (7%) stopped haloperidol -prolonged QTc-time (n = 9) -signs of Parkinsonism (n = 1) -renal failure (n = 1) - suspected malignant neuroleptic syndrome but later not confirmed (n = 1) None of the 9 prolonged QTc patients developed any tachyarrhythmia during the prolonged QTc-time period. **Comments:** When delirium was not detected with the CAM-ICU, but delirium was suspected based on medical and nursing reports, patients were additionally screened by a delirium expert according to the DSM-IV criteria. Potential side-effects of haloperidol were observed only when spontaneously reported and mild extrapyramidal side-effects may have been missed, although daily thorough physical examination of all patients is the usual care in the ICU. Patients who were not preventively treated according to the delirium prevention protocol, mostly due to non-compliance, served as an additional control group. Although this group showed similar patient characteristics as the historical control group and the prophylactic treated intervention group, the outcome measures in this group were comparable with the historical control group. This supports the beneficial effects of prophylactic treatment with haloperidol.
		n = 299 Control group (2008-2009) Men and women (39%) Mean age 64 ± 14 Historical cohort group of patients with a determined risk of 50% or more for delirium who were not treated with haloperidol for preventive reason.	**Subgroup analysis** highest risk for delirium **Non-treated patients during the implementation period**	benefit most from the haloperidol treatment no demographic differences between the control group and this non-treated group The incidence of delirium, unplanned removal of tubes and re-admission rate was significantly higher and the number of delirium free days was significantly lower in the non-treated group compared with the treated intervention group. **(See PDF)**	
Conclusion: Our evaluation study suggests that prophylactic treatment with low dose haloperidol in critically ill patients with a high risk for delirium probably has beneficial effects. These results warrant confirmation in a randomized controlled trial.					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	Baseline characteristics had significant differences
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	Observational study
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	Observational study
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Before-after study Authors discuss possible confounders based on non-compliant previously treated patients
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 4**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

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  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G2-Prakanrattana U, Prapaitrakool S. Efficacy of risperidone for prevention of postoperative delirium in cardiac surgery. Anaesth Intensive Care. 2007;35(5):714-9.

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects Comments
			Measure	Outcome	
Prakanrattana 2007 **Thailand** **Setting** University Hospital **Study Design** RCT (double-blind, placebo-controlled) **Randomization method** Computer generated number **Study Length/Start-Stop Dates** Not described **Purpose** To evaluate the potential of risperidone to prevent postoperative delirium following cardiac surgery with cardiopulmonary bypass and the secondary objective was to explore clinical factors associated with postoperative delirium. **Funding source(s):** Not disclosed **Quality Score** 5 **Risk of Bias**: Unclear	**N = 126** n = 63 risperidone n = 63 placebo n = 27 delirium n = 99 no delirium **Inclusion** Age >40 yrs undergoing elective cardiac surgery with cardiopulmonary bypass **Exclusion** N = not described Underwent emergency surgery Admitted to ICU before arriving at operating room Pre op delirium Hx psychiatric problems	**n = 63 Risperidone 1.0 mg** Men and women (42.8%) Mean age 61.3 (9.7) 1 mg of risperidone or placebo sublingually when the patients wake up in ICU.	**Delirium assessment:** CAM-ICU **Baseline characteristics** **Primary outcomes** Incidence of delirium **Secondary outcomes (NS)** Length of ICU stay Length of hospital stay **Risk Factors:** Age Time from opening eyes to following commands NYHA functional class (2/3/4) Post op renal failure Post op Respiratory failure Tracheal re-intubation Length of ICU stay Length of hospital stay **Factors associated with postoperative delirium** Age NYHA Functional class 1-2 3-4 Time from opening eyes to following commands ≤70 min >70 min Postoperative respiratory failure Postoperative renal failure	CAM -ICU rated by trained ICU nurse twice daily (between 8 a.m. and 18 p.m) in the ICU and once daily at 18:00 pm after discharged from ICU; severity and inter-rater reliability not described No significant difference between groups **Risperidone (63) vs placebo (63)** 11.1% vs. 31.7%, P=0.009 RR = 0.35, (0.16-0.77); NNT = 4,.85 3.3 (2.3) vs 3.2 (1.9), p=0.88 10.5 (6.1) vs 10.3 (4.4), p=0.574 **Delirium (27) vs No delirium (99)** 64.2 (6.6) vs 60.2 (10.3), p=0.017 112.2 (91.8) vs 61.97 (57.4), p=0.002 13/14/0 vs 7/27/1, p=0.50 4 (14.8%) vs 1 (1%), p=0.007 5 (18.5) vs 1 (1.0), p=0.002 4 vs 0, p=0.002 4.7 (3.6) vs 2.8 (1.4), p=0.002 13.3 (8.4) vs 9.6 (3.8), p=0.004 **Multiple logistic regression OR (CI), p** 1.04 (0.98-1.09), 0.214 0.289 1.00 1.73 (0.63-4.77) 0.003 1.00 4.57 (1.66-12.59) 13.78 (1.15-165.18), 0.038 13.89 (0.99-197.26), 0.052	**Adverse Effects** **Risperidone vs placebo** Significant difference Tracheal re-intubation: 0 vs 4, p=0.019 No significant difference Renal failure: 2 vs 3, p=1 Respiratory failure: 2 vs 4, p=0.68 Arrhythmia: 6 vs 6, p=1 Re-operation: 2 vs 1, p=1 Cardiovascular instability: 3 vs 4, p=1 **Comments:** The early events after anesthesia are assumed to be important for developing post op delirium. Respiratory failure leading to cerebral hypoxemia may also be involved in pathophysiology of post op delirium.
		n = 63 placebo group Men and women (39.6%) Mean age 60.7 (9.8) Identical sublingual placebo not possible; Listerine strip substituted	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Secondary outcomes**	See above See above See above See above	
Conclusion: A single dose of risperidone administered soon after cardiac surgery with cardiopulmonary bypass reduces the incidence of postoperative delirium. Multiple factors tended to be associated with postoperative delirium, but only the time from opening eyes to following commands and postoperative respiratory failure were independent risk factors in this study.					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	Unclear	Blinded = patients, investigators, ICU nurses, (person placing sublingual drug or placebo not blinded)
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	Unclear	Exclusions not described in detail (no CONSORT flow chart)
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	Unclear	Funding source not disclosed
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = Unclear**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 5**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G2-Wang W, Li HL, Wang DX, et al. Haloperidol prophylaxis decreases delirium incidence in elderly patients after noncardiac surgery: a randomized controlled trial*. Crit Care Med. 2012;40(3):731-9.

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects Comments
			Measure	Outcome	
Wang W 2012 **China** **Setting** Multicenter (2) ICUs – Tertiary teaching hospitals. **Study Design** RCT (double-blind, placebo controlled) **Randomization method** Computer-generated randomization codes **Study Length/Start-Stop Dates** 6/2009 to 5/2010 **Purpose** To evaluate the efficacy and safety of short-term low-dose intravenous haloperidol for delirium prevention in critically ill elderly patients after noncardiac surgery. **Funding source(s):** Not disclosed **Quality Score** 6 **Risk of Bias**: High	**N = 1346 screened** n = 736 excluded N = 608 eligible n = 151 refused **N = 457 randomized (included in ITT analysis)** n = 229 haloperidol n = 228 placebo **Inclusion** >65 yrs ICU admission after noncardiac surgery **Exclusion** N = 889 (after screening/ eligibility) 311 Non-surgical patients 299 < 65 years 51 Prolonged baseline QTc 26 Terminally ill 22 Neurosurgery 18 Visual/hearing impairment 9 Parkinsonism 2 Neuromuscular disease 151 Refused **Follow-up** For 28 days after surgery for postoperative complications	**n = 229 haloperidol group** n = 3 failed to receive study drug (ITT-analyzed) Men 145 (63.3%) Mean age 74.0 (5.8) Body mass index: 24.1 (8.0) Haloperidol (0.5 mg intravenous bolus injection followed by continuous infusion at a rate of 0.1 mg/h for 12 hrs Postoperative analgesia routinely included patient-controlled epidural analgesia or patient-controlled intravenous analgesia. Supplemental analgesia was administered with fentanyl if necessary For all patients, multicomponent approaches to reduce risk factors of delirium as suggested by Inouye et al (1999, 2006) were included in routine care.	**Delirium assessment:** RASS CAM-ICU **Baseline characteristics** **Significant differences for perioperative variables** Mean duration of anesthesia (hr) Mean duration of surgery (hr) Median total intra-op infusion (ml) **Primary outcomes** Incidence of delirium within 7 days after surgery Daily prevalence of delirium POD1 POD 3 Risk for postoperative delirium **Efficacy outcomes** Time to onset of delirium (hr) Number of delirium-free days Coma or delirium Median length of ICU stay (hr) Coma-free and delirium-free Incidence of non-delirium complications within 7 days Development of non-delirium compilations within 28 days **Subgroup analysis (risk for Delirium)** Intra-abdominal surgery	Level of sedation assessed using RASS (if patient unarousable assessment repeated later or noted as comatose. CAM-ICU administered by trained physician daily (from 4:00 PM to 6:00 PM) in either the ICUs or the general wards days 1 – 7. Delirium severity and inter-rater reliability were not discussed. No significant difference between groups **Haloperidol vs placebo** 5.51 (2.55) vs 4.81 (2.34), p= .003 4.51 (2,.42) vs 3.79 (1.13), p=.001 2700 (2000-4000) vs 2550 (1600-3675), p =.048 15.3% vs 23.2% , p =.031 7% vs 13.2%, p=.028 1.7% vs 5.3%, p=.041 OR (CI), p 0.574 (0.352-0.937), p=.026 6.2 (5.9–6.4) vs 5.7 (5.4–6.0),p=.021 6.8 (0.5) vs 6.7(0.8), p= .027 15.7% vs 23.7%, p.032 19.6 (16.3-22.9) vs 41.4 (39.3-43.5), p.006 6.8 (0.7) vs 6.7 (0.9), p=.030 4 (11.4%) vs 16 (30,.2%), p.040 6 (17.1%) vs 19 (35,8%), p=.057 14.5% vs 24.7%, p=.018	**Adverse effects:** No significant difference between groups for adverse effects related to delirium -Arrhythmia during infusion -change of heart rate-corrected QT interval after study drugl infusion -significant heart rate-corrected QT interval prolongation after study drug infusion -episode of extrapyramidal symptoms -RASS at end of study drug infusion -time to extubation -all cause 28 d mortality **Comments:** Apart from decreased incidence of postoperative delirium, it was found that the time to onset of delirium was significantly prolonged (mean, 0.5 day longer) and the number of delirium-free days was significantly increased (mean, 0.1 day more) by haloperidol prophylaxis. Because haloperidol can relieve certain symptoms of delirium (agitation or hyperactive symptoms), it is possible that patients receiving haloperidol might temporarily have their delirious symptoms masked during and immediately after the period of drug infusion, thus increasing the measure of delirium-free time. Limitations -no baseline cognitive tests -intraoperative parameters were different -placebo delirium incidence lower than anticipated
		n = 228 placebo group n = 1 failed to receive study drug (ITT-analyzed) Men 143 (62.7%) Mean age 74.4 (7.0) Body mass index: 23.5 (3.7) placebo (normal saline)	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Secondary outcomes**	See above See above See above See above	

Conclusion: For elderly patients admitted to intensive care unit after noncardiac surgery, short-term prophylactic administration of low-dose intravenous haloperidol significantly decreased the incidence of postoperative delirium. The therapy was well-tolerated.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	Significant differences in intraoperative parameters
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	1	Low	
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Significant baseline imbalances Funding not disclosed
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 6**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G2-Kaneko T, Cai J, Ishikura T, et al. Prophylactic consecutive administration of haloperidol can reduce the occurrence of postoperative delirium in gastrointestinal surgery. Yonago Acta Med. 1999;42(3):179-84.

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects
			Measure	Outcome	
Kaneko 1999 **Japan** **Setting** University Hospital **Study Design** randomized, comparative clinical study **Randomization method** The randomization was conducted by way of a closed envelope system **Study Length/Start-Stop Dates** 4/1995 to 8/1998 5 days **Purpose** To assess the effectiveness and safety of the use of haloperidol for the reduction of postoperative delirium **Funding source(s):** Not described **Quality Score** 4 **Risk of Bias**: High	**N = 78** n = 38 haloperidol n = 40 normal saline . **Inclusion** Elective GI surgery Admitted to High and ICU 1 or 2 weeks before scheduled surgery Oral consent **Exclusion** N = not described No criteria provided **Post admission testing** Interview Clinical exam Laboratory testing	**n = 38 haloperidol group 5 mg iv** Men/women: 24/14 Mean age 72.4 ± 8.2 5 mg of haloperidol in 1.0 mL intravenously postoperatively at 21:00 for 5 consecutive days	**Delirium assessment:** DSM-III-R **Baseline characteristics** Ischemic heart disease Hypertension Respiratory disease Diabetes mellitus Liver disease Cognitive impairment **Primary outcomes** incidence of delirium **Secondary outcomes** Intensity and duration of delirium average and total time of sleep ratio of sleep time during the day and night Use of haloperidol and flunitrazepam potential confounders for delirium incidence	RAs rated cog test and sleep pattern, delirium were determined if DSM-III-R criteria met on day 5. Inter-rater reliability and delirium severity were not discussed. **Haloperidol vs Normal saline** **N = 38 vs 40** No significant difference between groups 5 (13.2%) vs 8 (20.0%) 13 (34.2%) vs 12 (30.0%) 6 (15.8%) vs 4 (10.0%) 9 (23.7%) vs 12 (25.0%) 3 (7.9%) vs 6 (15.0%) 2 (5.3%) vs 4 (10.0%) 4/38 vs 13/40 , p <0.05 control group symptoms were severe and longer no significant difference in 2 groups lower during the use of haloperidol higher in haloperidol group No significant difference between groups for postop drugs, method of pain control, hypoxia or infection	No extrapyramidal side effects n = 1 transient tachycardia (haloperidol group)
		n = 40 normal saline group Men/women: 26/14 Mean age 73.1 ± 9.3 normal saline intravenously postoperatively at 21:00 for 5 consecutive days	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Secondary outcomes**	See above See above See above See above	
Comments: This prospective study is the first systematic evaluation of the use of prophylactic administration of intravenous haloperidol to reduce the occurrence of postoperative delirium. The mechanism by which haloperidol reduces the occurrence of postoperative delirium is not clear. Some studies suggest that actions other than the blockade of central dopamine receptors may be responsible for haloperidol's calming effect in patients with delirium.					
Conclusion: These results suggest that daily postoperative administration of haloperidol can reduce the occurrence of postoperative delirium safely.					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	Unclear	Not described
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	High	Exclusion criteria not described
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	No ITT analysis Funding not disclosed
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	0		Intervention/control groups <50
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 4**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
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  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G2-G4-Page VJ, Ely EW, Gates S, et al. Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (Hope-ICU): a randomised, double-blind, placebo-controlled trial. Lancet Respir Med. 2013;1(7):515-23.

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects
			Measure	Outcome	
Page VJ 2013 **UK** **Setting** ICU – general adult **Study Design** RCT (double-blind, placebo-controlled) **Randomization method** Independent nurse, in 1:1 ratio, with permuted block size of four and six, using a centralized, secure web-based randomization service **Study Length/Start-Stop Dates** Up to 28 days 11/9/2010 to9/21/2012 **Purpose** To establish whether early treatment with haloperidol would decrease the time that survivors of critical illness spent in delirium or coma. **Funding source(s):** National Institute for Health Research **Quality Score** 8 **Risk of Bias**: Low	**N = 677 assessed for eligibility** n = 535 excluded (see below) **N = 142 randomized** n = 71 haloperidol n = 71 placebo **N = 141 analyzed** **Inclusion** Critically ill patients ⩾18 years mechanical ventilation within 72 h of admission **Exclusion** N = 535 114 expected to be discharged within 48 h of admission 107 declined to participate 97 moribund, unlikely to survive more than 48 h 49 undergone uncomplicated elective surgery 37 more than 72 h from admission 28 QTc more than 500 ms on current ECG 28 already on antipsychotics 24 moderate to severe dementia or cognitive impairment 23 structural brain damage 17 language difficulty: learning or English language disability 7 Parkinson's disease 6 previously participated in Hope-ICU 2 haloperidol allergy 1 younger than 18 years 15 others	**n = 71 haloperidol group** 1 – lost to follow up **n = 71 analyzed** Men 37 (52%) Mean age 67·9 (16·5) Time from ICU admission to randomisation: 0·9 (0·91) Treatment was initiated within 72 h of admission to ICU. Patients received haloperidol 2·5 mg or placebo intravenously every 8 h, irrespective of coma or delirium status. The first dose was given at either 8 am, 4 pm, or midnight, depending on the time of randomisation. Study drug was discontinued on ICU discharge, once delirium-free and coma free for 2 consecutive days, or after a maximum of 14 days of treatment, whichever came first. Patients, clinical staff and research staff blinded	**Delirium assessment:** CAM-ICU RASS **Baseline characteristics** **Primary outcomes** Alive, delirium-free, and coma-free days in first 14 days **Secondary outcomes** Days in delirium in first 14 days Days in coma in fi rst 14 days Alive, delirium–free,coma-free days in first 28 days Days in delirium in first 28 days Days in coma in fi rst 28 days 0 Ventilator-free ds in first 28 ds Mortality at 28 days Length of critical care stay (days) Length of hospital stay (days) **Secondary data analysis** RASS ≥ +2	Bedside nurse assessed RASS of –2 to +4, and then performed CAM-ICU twice during each 12 h shift with a mini of 4 h. No significant difference between groups **Haloperidol vs placebo** 5 (0–10) vs 6 (0–11); p=0·53 RR: –0·48 (–2·08 to 1·21) 5 (2–8) vs 5 (1–8) p=0·99 0 (0–2) vs 0·5 (0–2) p=0·99 19 (0–24) vs 19·5 (0–25) p= 0·57 5 (2–10) vs 5 (1–9) p= 0·71 0 (0–2) vs 1 (0–2) p=0·90 21 (0–25) vs 17 (0–25) p=0·88 20 (28·2%) vs 19 (27·1%) RR 1·04 (0·61 to 1·77) 9·5 (5–14) vs 9 (5–18) p=0·47 18·5 (12–31) vs 26 (15–40) p=0·54 No significant difference between groups in primary analysis 13% (8.75-17.00) vs 20% (17.5-26.75) p=0.0075	**Haloperidol vs placebo** Serious Apnea post treatment for agitation 0 vs 1 (3%) Fast atrial fibrillation with hypotension 1 (3%) vs 0 Readmission to ICU with sepsis 1 (3%) vs 1 (1%) Failed extubation 1 (3%) vs 3 (4%) Oversedation: 11 vs 6 QTc prolongation: 7 vs 6 Drop out: 1 vs 1 **Reasons for study drug termination:** 2 days CAM-ICU negative 20 (28%) vs 26 (37%) Discharge from ICU 17 (24%) vs 12 (17%) Oversedation 8 (11%) vs 5 (7%) QTc ≥500 msec 7 (10%) vs 4 (6%) Died 5 (7%) vs 4 (6%) Discontinuation of active treatment 3 (4%) vs 7 (10%) 14 days after randomisation 3 (4%) vs 6 (9%) Extrapyramidal symptoms 0 vs 1 (1%) Other 8 (11%) vs 5 (7%)
		n = 71 placebo group 1 – lost to follow up 1 – discontinued **n = 70 analyzed** Men 45 (64%) Mean age 68·7 (14·9) Time from ICU admission to randomisation: 0·88 (0·81) 0.9% saline i.v. same protocol as above	See above	See above	

Comments: Defining normal cognitive function as the absence of delirium and coma in a patient is an inevitable constraint because it is not possible to be confident in delineating the cause of coma as disorder or drugs in many ICU patients. Patients who died within 14 days were assessed with zero delirium-free, coma-free days to manage the possible conflicting effects of haloperidol on delirium and survival in the same way that days alive and free from mechanical ventilation are used as an outcome measure in treatments for adult respiratory distress syndrome

Conclusion: These results do not support the hypothesis that haloperidol modifies duration of delirium in critically ill patients. Although haloperidol can be used safely in this population of patients, pending the results of trials in progress, the use of intravenous haloperidol should be reserved for short-term management of acute agitation.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	1	Low	
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	1	Low	
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = Low**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 8**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G2-Vochteloo AJ, Moerman S, van der Burg BL, et al. Delirium risk screening and haloperidol prophylaxis program in hip fracture patients is a helpful tool in identifying high-risk patients, but does not reduce the incidence of delirium. BMC Geriatr. 2011;11(2318):39

Study Characteristics	Population	Study Groups	Results		Comments
			Measure	Outcome	
Vochteloo AJ 2011 Netherlands **Setting** Teaching Hospital **Study Design** Prospective cohorts (Observational study) **Selection method** A series of consecutive admissions; patients based on Risk Model for Delirium (RD score) (⩾ 5 as a high-risk group, and < 5 as a low risk group) **Study Length/Start-Stop Dates** 1/2008 to 12/2009. 2005-2007 **Purpose** To determine whether using prophylaxis would diminish delirium incidence in hip fracture patients; and to investigate the value of the RD score and differences between low- and high-risk patients in delirium incidence, length of stay, return to pre-fracture living situation and mortality. **Funding source(s):** No funding **Quality Score** 3 **Risk of Bias**: High	**N = 445** n = 67 excluded (RD score completed incorrectly) **N = 378 evaluated** **Inclusion** Age>65 Hip fracture -low energy trauma **Exclusion** N = not described Hip fracture with pathologic origin **All patients prospective evaluation** At admission -standard procedure and recording During follow up -in hospital -3 months -12 months **Risk Model for Delirium** Predisposing risk factors -delirium during previous hospitalization -dementia -clock drawing (small or big mistakes) -Age (70-85; >85) -impaired hearing -impaired vision -ADL problems -use of heroin, methadone or morphine -daily consumption of 4 or more alcoholic beverages	**n = 173 high-risk (⩾ 5) group** Women 79.2% Mean age 86.6 ± 6.5 Other The Risk Model for Delirium was designed with a cut-off point of 5; patients scoring 5 or more points were considered high-risk patients. The high risk group was prescribed 1 mg haloperidol 2 x day for delirium prophylaxis When patients developed a delirium, they were fully assessed to exclude a somatic cause and treated by the psychiatric department.	**Delirium assessment:** DSM IV **Baseline characteristics** Dementia ASA -III-IV Institutional residence Having no partner Psychotropic drug use Spinal/epidural anesthesia **Primary outcomes** delirium incidence **Secondary outcomes** Length of stay ⩾ 10 days Alternative living situation at 3 months* In-hospital mortality 3-month mortality 12-month mortality	Doctors and nursing staff rated delirium symptoms during their daily rounds and assessments (No cognitive testing) **high-risk vs low risk group** 51.4% vs 0% RR: 3.44 (2.87-4.12) p< 0.001 45.7% vs 22.9% RR: 1.68 (1.36-2.07) p < 0.001 61.8% vs 10.2% RR: 3.17 (2.54-3.95) p< 0.001 79.3% vs 60.9% RR: 1.74 (1.26-2.41) p< 0.001 51.4% vs 24.4% RR: 1.82 (1.47-2.25) p< 0.001 97.5% vs 91.1% RR: 2.26 (1.05-4.85) p= 0.006 42.4% vs 14.1% RR: 1.98 (1.62-2.41) p< 0.001 65.1% vs 44.1% RR: 1.61 (1.27-2.05) p< 0.001 62.3% vs 17.0% RR: 4.25 (2.65-6.80) p< 0.001 5.8% vs 2.0% RR: 1.60 (1.12-2.26) p= 0.050 23.1% vs 8.3% RR: 1.69 (1.37-2.10) p< 0.001 37.0% vs 14.6% RR: 1.77 (1.45-2.17) p< 0.001	**Adverse effects not described** **Comments:** **Multivariable analysis:** The RD-score was a significantly contributing variable for delirium, length of stay and alternative living situation at 3 months. Age and ASA classification were strong independently contributing variables as well. The RD-score had a moderate sensitivity (71.6%) and specificity (63.8%) The negative predictive value (NPV) of a score < 5 was quite high (85.9%), which is very important as a screening instrument should have a high NPV. The consequence of a false positive test (i.e. prophylactic treatment with low-dose haloperidol in a non-delirious patient) is generally modest as very few side effects of a low dose of haloperidol can be expected. Therefore, its moderate positive predictive value (42.2%) is of lesser importance. Delirium was diagnosed based on clinical examination, as stated in the DSM IV. However, the author did not use a cog test before.
		n = 205 low- risk (< 5) group Women 69.3% Mean age 81.4 ± 7.1 No prophylaxis protocol	**Historical comparison** age male delirium incidence (vs 2005) delirium incidence (vs 2006) delirium incidence (vs 2007)	**prospective (2008-2009) vs historical (2005-2007)** 83.7 vs 82.9 (P = 0.082) 26.2% vs 24.3% (P = 0.515) 27% vs 29.0% (P = 0.28) 27% vs 23.9%, P = 0.81 27% vs 27.8%, P = 0.44	
Conclusion: Prescribing prophylactic haloperidol to high risk patients as identified by the Risk Model for Delirium did not reduce delirium incidence in a cohort of hip fracture patients. The RD score did prove to be an accurate tool for identifying high risk patients with poorer outcome regarding delirium incidence, length of stay and return to pre-fracture living situation.					

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	Significant baseline differences Observational study
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	Observational study
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	Observational study
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	High	Patients not eligible due to incorrect RD scoring 67/445 (15%)
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Extreme baseline imbalances Probable confounders (delirium vs cognitive impairment) Historical groups were not scored by RD model
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 3**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G2 Kalisvaart KJ, de Jonghe JF, Bogaards MJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. J Am Geriatr Soc. 2005;53(10):1658-66.

Study Characteristics	Population	Intervention Groups	Results		Adverse Effects
			Measure	Outcome	
Kalisvbaart 2005 **The Netherlands** **Setting** Medical school affiliated hospital **Study Design** RCT-double blind, placebo controlled **Randomization method** Systematic screening of new admissions; sequential assignment by computer generated code; research team/participants blinded; checked by interviewing assessors **Study Length/Start-Stop Dates** 8/2000 to 8/2002 Duration 1 to 6 d (based on onset of delirium) **Purpose** To assess the effectiveness of 1.5 mg haloperidol daily versus placebo on the primary (incident delirium) and secondary (deterioration of delirium) prevention of postoperative delirium in hip surgery patients. **Funding source(s):** The medical center funded this study **Quality Score** = 7 **Risk of Bias** = Unclear	**N = 430** n = 212 intervention n = 218 placebo **Inclusion** Age ≥70 Acute or elective hip surgery Intermediate or high risk for postop delirium* **Exclusion** N = 78 (list in PDF) Delirium at admission No risk factors at admission Hx haloperidol allergy Use of cholinesterase inhibitors Parkinsonism Epilepsy Levodopa tx Profound dementia Language barrier Intubation Respiratory isolation Aphasia Coma Terminal illness Delay of surgery >72 h Prolonged QTc interval -≥470 ms women -≥460 ms men ***Risk Factors** Visual impairment worse than 20/70 after correction Severity of illness ≥16 - APACHE II Cognitive impairment ≤24 -MMSE Index of dehydration ≥18 -ratio of blood urea nitrogen to creatinine *Intermediate risk* -presence of 1 or 2 risk factors *High risk* -presence of 3 or more risk factors *Low risk patients were assessed daily according to the protocol for incident delirium but received no prophylactic medication	**n = 212 (0.5 mg 3 x day)** n = 179 intermediate risk n = 33 high risk Men and women (81.1%) Mean age 78.71 (6.04) **Intervention** Trial medication started on admission and continued until 3 d after surgery All patients assessed daily for efficacy and safety Geriatric nurses and geriatricians provided proactive geriatric consultation on all patients -structured multimodular protocol (see PDF) If postop delirium occurred -treatment according to standard procedures -haloperidol 3 x d or -lorazepam 3 x d -or both in increasing doses depending on delirium sx -assessed for severity and duration In case of emergency: independent physician could request unmasking Adherence recorded daily Daily assessments -MMSE -DRS-R-98 -Digit Span Test	**Delirium assessment:** DSM-IV Confusion Assessment Method (CAM) DRS-R-98 **Baseline characteristics measures** MMSE Informant Questionnaire on Cognitive Decline in the Elderly Snellen test APACHE II Blood urea nitrogen/creatinine Geriatric Depression Scale Barthel Index **Primary outcomes (postop days 1-3)** Incident delirium **Secondary outcomes (postop days 1-3)** Highest delirium rating score Mean difference Duration of delirium (days) Mean difference Length of hospital stay Mean difference	Daily rating of CAM and DSM IV based on MMSE, DRS, digit spans DRS for delirium severity Haloperidol vs placebo No significant difference between groups in baseline characteristics No difference between groups Minimal both groups Some impairment both groups Overall relatively good clinical condition (low scores) Light dehydration both groups Low both groups High scores both groups N = 201 Haloperidol vs placebo N = 32 vs 36 patients 15.1% vs 16.5% RR 0.91 (0.59 to 1.44) Haloperidol vs placebo 14.4 ± 3.4 vs 18.4 ± 4.3 4.0 (2.0 to 5.8), p <.001 5.4 ± 4.9 vs 11.8 ± 7.5 6.4 (4.0 to 8.0), p <.001 17.1 ± 11.1 vs 22.6 ± 16.7 5.5 (1.4 to 2.3), p <.001	Unmasking = 2 Dropouts n = 20 -n = 3 in compliance -n = 3 withdrew consent -n = 11 protocol violation -n = 3 adverse events Lost to follow up n = 11 No drug related side effects were seen through the study period Adverse events were never related to extra-pyramidal symptoms No sedation reported
		n = 218 placebo (3 x d) n = 181 intermediate risk n = 35 high risk n = 2 no risk Men and women (78.9%) Mean age 79.57 (6.27)) **Intervention** (see above)	**Delirium assessment:** **Baseline characteristics measures** **Primary outcomes** See above **Secondary outcomes** See above	See above See above N = 194	Unmasking = 5 Dropouts n = 28 -n = 4 in compliance -n = 6 withdrew consent -n = 7 protocol violation -n = 8 adverse events (not described) -n = 3 randomization violation Lost to follow up n = 24

Comments: Haloperidol patients with delirium continued to have significantly lower severity scores on days 5-8. The findings of the current study may indicate a "priming" effect (i.e., therapeutic blood serum levels of haloperidol were reached sooner once treatment of delirium was started).

Conclusion: Low-dose haloperidol prophylactic treatment demonstrated no efficacy in reducing the incidence of postoperative delirium. It did have a positive effect on the severity and duration of delirium, Moreover, haloperidol reduced the number of days patients stayed in the hospital, and the therapy was well tolerated.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	1	Low	
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	1	Low	
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	1	Low	
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	Unclear	High number of dropouts (>10%; 9% Haldol; 13% placebo) 8 adverse events in placebo not described
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	1	Low	Did do ITT analyses; impact unclear
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = Unclear**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 7**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

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  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G5-Bee Gek Tay L, Chew Chan MP, Sian Chong M**.** Functional improvement in hospitalized older adults is independent of dementia diagnosis: experience of a specialized delirium management unit. J Hosp Med. 2013;8(6):321-7.

Study Characteristics	Population	Intervention Groups	Results		Comments
			Measure	Outcome	
Bee Gek Tay L 2013 Singapore **Setting** Geriatric Monitoring Unit (GMU) **Study Design** Prospective cohort **Selection method** Admissions to GMU meeting inclusion criteria **Study Length/Start-Stop Dates** 11/2010-11/2011 **Purpose** To examine the influence of a multicomponent delirium management program (the Geriatric Monitoring Unit – GMU) on functional progress of delirious older patients and the impact of underlying dementia on functional recovery. **Funding source(s):** Ministry of Health Quality Improvement Funding **Quality Score** 3 **Risk of Bias**: High	**N = 146** n = 24 excluded **N = 122 analyzed** n = 82 dementia present n = 40 dementia absent **Inclusion** Age ≥65 Admitted to geriatric medicine department Delirium dx at or after admission (CAM) **Exclusion** N = 24 n = 17 respiratory or infection control precautions or critical illness n = 7 repeat admission Medical illness requiring special monitoring -telemetry (afib or MI) Coma Terminal illness Unable to communicate Severe aphasia Severely combative (risk of harm to self, staff, others) Contraindications to bright light therapy Refusal of GMU admission (by patient, family or attending physician) **Assessments (all patients)** Cognitive eval by geriatrician Medical records review DSM-IV criteria for dementia Delirium subtype by geriatrician At admission -comprehensive med hx -physical exam -lab tests and imaging Charlson comorbidity Index Severity of Illness Index Modified Barthel Index (MBI)	**n = 82 dementia present** Men and women (64.6%) Mean age 84.2 (7.4) **GMU core interventions (structured protocols)** -early mobilization -avoidance of physical restraints -avoidance of chemical restraints if possible -daily review of need for -IV -catheter -supplemental oxygen -daily orientation (3 x d) -therapeutic activities (3 x d) -PT and OT sessions -sensory impairment corrections -bright light therapy (other sleep enhancement measures) Functional independence definitions (MBI score) -total dependence (0-20) -severe dependence (21-60) -moderate dependence (61-90) -slight dependence (91-99) -full independence (100)	**Delirium assessment:** CAM Abbreviated Mental Test (AMT) C-MMSE DRS – 98-rev CAM-sev **Baseline characteristics** CAM-sev Charlson score (trend) Precipitating cause Dementia present most common Dementia absent most common **Primary outcomes** Average duration of delirium Mean LOS (all hospital days) Cognitive improvement after recovery AMT scores (mean) CMMSE (mean) Functional performance gain MBI (mean) at discharge **Improvement/change at discharge** AMT AMT change CMMSE CMMSE change DRS-sev DRS-sev change CAM sev CAM-sev change Functional outcomes MBI and MBI change Progress to less dependent	Baseline and daily assessments of all measures listed by a trained assessor from the time of admission until discharge from the GMU **Significant differences between groups** **Dementia present vs absent** 4.74 (1.47) vs 5.23 (1.17), p 0.07 2.27 (1.24) vs 1.75 (1.63), p 0.054 Overall p 0.050 between groups Pneumonia = 28.0% vs 7.5% UTI = 32.9% vs 42.5% **All patients (present + absent)** 8.2 days 17.0 days 1.44 (2.38), p <0.001 3,54 (5.61), p <0.001 n = 48% progressed to less dependent category 19.42 (17.1) p <0.001 **Dementia present vs absent** 2.29 (2,58) vs 5.20 (2.88), p <0.001 +0.61 (1.70) vs +3.15 (2.68), p <0.001 7.34 (6.64) vs 11.90 (6.16), p <0.001 +1.99 (4.87) vs +6.73 (5.74), p <0.001 18.00 (6.74) vs 14.45 (6.90), p 0.008 -8.17 (7.25) vs -12.05 (6.43), p 0.001 NS (p 0.13) -2.17 (1.68) vs -3.08 (1.67), p 0.006 NS (0.22 and 0.35) NS (1.00)	Early recognition of delirium and actively addressing all predisposing and precipitating factors, along with emphasis on rehabilitation in a multidisciplinary unit, appear to be important factors contributing to the positive functional outcomes in these patients. None of the patient admitted to the GMU had been subject to physical restraint. This study lacks data on longer term outcomes following delirium resolution. In this study, pre-existing dementia did not preclude delirious patients from functional improvement. In addition, patients with dementia -did not take longer to recover from delirium -did not appear to a longer duration for making similar functional gains -did not require a longer LOS Unable to adjust for premorbid functional status at admission
		n = 40 dementia absent Men and women (55%) Mean age 84.0 (8.1) **GMU core interventions as above**	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Predictors of functional recovery at discharge** Female Hypoactive delirium vs hyperactive delirium Severity of illness	See above See above See above **Multivariate analysis (all patients)** P 0.009 P 0.001 P 0.003	

Conclusion: Elderly patients with dementia recovering from delirium have comparable potential for function recovery as their cognitively intact counterparts in a delirium management unit focused on geriatric nursing care and rehabilitation.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	Significant differences between groups at admission
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	NA – prospective cohort
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	NA – prospective cohort
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Baseline significant differences Unclear possible confounders
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	0		Dementia absent = 40
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 3**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
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  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G5-Eeles E, Thompson L, McCrow J, Pandy S. Management of delirium in medicine: experience of a Close Observation Unit. Australas J Ageing. 2013;32(1):60-3.

Study Characteristics	Population	Intervention	Results				Comments
			Measure	Outcome			
Eeles E 2013 **Setting** Hospital – general medicine and special unit **Study Design** Observational: before and after design **Selection method** Historical controls from chart review; 2011 prospective cohort based on inclusion criteria **Purpose** To develop and evaluate a new model of care for the management of patients with delirium who are at risk to themselves through behavioral or psychiatric disturbance **Funding source(s):** Not described **Quality Score** 3 **Risk of Bias**: High	**N = 175 2010 (usual care control)** **N = 237 2011** n = 132 usual care n = 105 COU **Inclusion** Diagnosis of delirium (CAM) Score >2 on PAS -agitation -aggression -vocalization -resistiveness Falls score >21 **Inclusion (2010 controls**) ICD-10 diagnostic code for delirium dx Admitted to internal medicine services **Exclusion** N = not described Primary dx of a mental health problem	**Usual care** -admission from ED -general medical ward -management by ward staff -5 RNs -1 nursing assistant (AIN) -delirium with risky behavior = 1:1 AIN **Close Observation Unit (COU)** -conversion to 4 bed unit -trained AINs (full day) -Nurse educator = trainer -definitions for delirium and dementia -environmental considerations -communication styles -practice partnership models of care -operations of COU **COU staffing** -RN oversight -AIN 1:4 patients (continuous) **COU protocols** -hourly behavioral observations -Pittsburgh Agitation Scale (PAS) -Pain Assessment in Advanced Dementia Scale (PAADS) -targeted nursing interventions -toileting -nutrition -diversion activity -mobility -reduced stimuli -patient environment adapted -wall clock -orientation reminders -patient biography -safer environment changes -high/low profile beds -split rails -height adjustable arm chairs Discharge -falls risk to low or moderate -absence of neuropsychiatric disturbance (PAS = 0) for 24 h		**2010** **7/2010-11/2010** **N = 175**	**2011** **7/2011-11/2011** **N = 237** **n = 132 no COU (usual care)**	**COU** **n = 105** n = 100 delirium dx	A dedicated unit, with advantages of continuity of care, may share more features with preventive approaches. Using standard measures to attempt to identify those immediately at greatest risk (through falls and neuropsychiatric disturbance) and proactively managing these problems ameliorates the proximal threat.. The weak sensitivity and specificity suggests that concordance between case-finding methods is far from ideal. Studies of delirium should also try and measure, and screen for, dementia.
			Delirium assessment: COU only CAM Pittsburg Agitation Rating Scale (PAS)	Retrospective review of coding in medical chart		Nurse assessment using CAM and PAS (>2) at study entry	
			Age (mean SD)	79.6 (11.1)	80.0 (10.4)	80.3 (11.3)	
			Gender (women)	51%	51%	43%	
			Mean LOS (SD)	24.7 (36.0)	21.7 (39.5)	22.7 (28.5)	
			Falls in hospital n (%) Yes No	n = 165* 5 (3.0%) 160 (97.0%)	n = 187* 6 (3.0%) 181 (97.0%)	 3 (3.0%) 102 (97.0%)	
			Died in hospital n (%) Yes No	n = 165* 25 (15.0%) 140 (85.0%)	n = 187* 10 (5.0%) 177 (95.0%)	 7 (7.0%) 98 (93.0%)	
			Discharged home n (%) Yes No	n = 172* 133 (77.0%) 39 (23.0%)	n = 187* 152 (81%) 35 (19.0%)	 80 (76.0%) 25 (24.0%)	
			Diagnosis of delirium (*retrospective coding*)	58%			
			Diagnosis of delirium (*prospective*)			86% Sensitivity 58% Specificity 86%	
			Reduction in mortality p = 0.002	n = 165* 15.0%	n = 187* 5%		
			*NOTE: reported n different than reported total (See Table 1, PDF)				

Conclusion: The COU employed a comprehensive and multifaceted approach targeting environment, nurse education and processes of care. Achievement of a reduction in mortality demonstrates that delirium can be managed effectively with an improvement in outcomes. There remains a clear clinical imperative for the prospective evaluation of new models of care in delirium.

QUALITY / RISK OF BIAS

RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	Authors indicate no significant difference between COU cohort and historical controls, but there was a significant difference in mortality (p = 0.002) Data did not differentiate between baseline and outcomes
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	NA – observational study
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	NA-observational study
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	High	2011 usual care' n for some reported outcomes differed from original N; withdrawals/dropouts not discussed
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Before/after design Historical controls Funding source not specified
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 3**

Instructions on rating:

- Quality score: Give one point for each of the 8 criteria above, where 0=bias or goal not achieved; 1=no bias or goal achieved (or score unclear). Each article should be assigned a **score from 0-8, where 8 indicates a high quality article.**

- Risk of Bias: Based on the criteria from 1-6 only, give a Cochrane rating of bias, as follows:
  - **Low** risk of bias: Low risk of bias on all 6 domains
  - **Unclear** risk of bias: High or unclear risk of bias on 1 or more of 6 domains
  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

G5-Flaherty JH, Steele DK, Chibnall JT, et al. An ACE unit with a delirium room may improve function and equalize length of stay among older delirious medical inpatients. J Gerontol A Biol Sci Med Sci. 2010;65(12):1387-92.

Study Characteristics	Population	Study Groups	Results		Comments
			Measure	Outcome	
Flaherty JH 2010 **USA** **Setting** Community-based hospital with an academic university affiliation **Study Design** Retrospective observational study **Selection method** Convenience sample patients admitted to the ACE Unit during the specified time frame **Study Length/Start-Stop Dates** 1/ 2008 to 4/2008 4 months **Purpose** To compare delirious patients with non-delirious patients on an Acute Care of the Elderly (ACE) Unit with a Delirium Room (DR) related to specific outcomes including change in function from admission to discharge, hospital length of stay and mortality. **Funding source(s):** Not disclosed **Quality Score** 3 **Risk of Bias**: High	**N = 355 admissions** n = 207 excluded **N = 148 met inclusion criteria** **Inclusion** Age ≥65 CAM within 24 hours of admission (performed by a physician) length of stay >48 h Admission from -emergency department -clinic -directly from home. **Exclusion** N = 207 Length of stay <48 h Transfer from another floor Transfer from ICU CAM not performed within 24 h of admission **Data source** Included patients' medical charts reviewed 3 individuals (1 study author) Standardized form developed by 2 investigators No blinding **Other Variables** ADLs (assessed by nurses) Calculated from chart review: -Acute Physiology and Chronic Health Evaluation score (APACHE) -Charlson Comorbidity Index scores (CCMI)	**n = 104 No Delirium** Men and women (73%) Mean age 83.2 (7.1) All patients admitted to the ACE Unit	**Delirium assessment:** Modified CAM (administered by 3 geriatricians and unit nurses) (modified CAM = Inouye 1999) **Baseline characteristics** **Primary outcomes** prevalence of delirium delirium incidence **Secondary outcomes** ADL, (admission to discharge, mean SD) Admitted from home but discharged to a facility LOS LOS,log10–transformed Died, % (n)	Trained geriatrician administered the CAM within the first 24 hrs of admission (8:00 am - 3:00 pm.) After admission, trained nurses performed modified CAM daily on days 1-6. Correlation between physician CAM and nurse CAM (r =.56, p <.001). Nurse performed CAMs yielded an intra-class coefficient of 0.65 and an alpha coefficient of 0.91. No significant difference between groups **No delirium vs delirium** 16.2% (24/148) 16.1% (20/124) **No Delirium vs delirium** 7.4 (4.7) to 6.9 (4.5) vs 4.1 (4.6) to 6.1 (3.9) <.001 23 (11/48) vs 40 (6/15) p=.197 5.9 (3.6) vs 6.4 (3.1) p=.461 0.71 (0.23) vs 0.76 (0.21), p=.281 1.9% (2) vs 4.5% (2), p=.582	In a multivariate analysis controlling for the covariates age, gender, Charlson Comorbidity Index, APACHE score and LOS, the ADL interaction effect remained statistically significantly. For the finding that patients with delirium improved function, there are at least two explanations. First, delirious patients had a lower mean ADL score on admission, which allowed this group the room to improve. Second, it is possible that with delirium, patients either lose function due to the delirium or nurses assessing ADL status give these patients a lower score because of the delirium. Then, as the delirium improves, so do ADL scores Limitations -not clear which part of the ACE unit or DR or both, could have led to a benefit -ACE Unit principles may have had an effect of delirium management -there is cross-over in nursing staff between the Unit and the DR -use of a convenience sample may have introduced selection bias -the study may have been underpowered to detect a significant difference in some of the outcomes of interest -there was not a control group of patients with delirium
		n = 44 Delirium Men and women (68%) Mean age 85.3 (5.7) All patients admitted to the ACE unit, but not all delirious patients were placed in the Delirium Room during their hospital stay. 43% spent at least some time in the Delirium Room -of these, 47% spent their entire hospitalization in the DR -31%spent 50% to <100% in the DR -21% spent <50% in the DR	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Secondary outcomes**	See above See above See above See above	

Conclusion: This study found that an ACE Unit with a Delirium Room may improve ADL function from admission to discharge among patients with delirium compared with those without delirium. Length of stay and mortality were similar among patients with and without delirium.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	No significant baseline differences but no matching between groups
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	Retrospective observational study
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	Retrospective observational study
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Study design – historical cohort Possibility of selection bias noted by authors Funding not described
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	0		n = 44 Delirium group
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 3**

Instructions on rating:

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  - **High** risk of bias: High risk of bias on 2 or more of 6 domains

REVISED 11/11/13

G5-Lu JH, Chan DK, O'Rourke F, et al. Management and outcomes of delirious patients with hyperactive symptoms in a secured behavioral unit jointly used by geriatricians and pyschogeriatricians. Arch Gerontol Geriatr. 2011;52(1):66-70.

Study Characteristics	Population	Study Groups	Results		Comments
			Measure	Outcome	
Lu JH 2011 **Australia** **Setting** University affiliated hospital **Study Design** Observational – retrospective **Selection method** Chart review of patients admitted / directly or transferred to the Unit **Study Length/Start-Stop Dates** 1/2002-10/2008 **Purpose** To examine the clinical outcomes and length of stay of two groups of delirious patients with hyper-active symptoms admitted to the geriatric/psycho-geriatric Unit (direct admission from the Emergency Department vs transferred from other inpatient services) In addition, to compare the management of challenging behavior and its outcome between the two groups. **Funding source(s):** Not described; no conflicts of interest disclosed **Quality Score** 4 **Risk of Bias**: High	**N = 144 delirium patients** n = 22 excluded (see below) **N = 122 included** n = 54 indirect admission n = 68 direct admission from ED Men and women (60.7%) Mean age 80.4 (7.0) Hyperactive delirium (82%) Residing at home (67.2%) Dementia (41.0%) Wanderer (63.1%) Charlson Comorbidity Index 2.0 (1.6) **Inclusion** Admission dx = delirium (per CAM and ICD-10) Dx confirmed by treating clinicians at admission n = 100 dx hyperactive delirium n = 22 dx mixed delirium **Exclusion** **N = 22** Recovery from delirium before admission n = 2 delirium developed during hospitalization n = 12 hypoactive delirium n = 8 no psychomotor disturbance **Avoidance of observational bias** Data collector was a visiting doctor with no clinical involvement **Uniformity of the data collection process** A random 20 sets of notes were counter-checked by 2 independent geriatricians and a senior research manager to ensure accuracy and consistency of interpretation of the clinical data	**n = 54 indirect admission (transferred from other wards)** Men and women (51.0%) Mean age 79.6 (7.2) Hyperactive delirium (83.3%) Residing at home (74.1%) Dementia (40.7%) Wanderer (70.4%) Charlson Comorbidity Index 2.1 (1.8) Patients transferred from other wards to Unit >24 h after admission	**Delirium assessment:** **Baseline characteristics** **Reasons for transfer to Unit** Wandering Aggression Other behavioral/psychological symptoms Other **Major causes of delirium** General illness/ infection CNS disorder Medications **Primary outcomes** Physical restraint Chemical restraint Discharged home Length of stay Duration of delirium Recovery from delirium Mortality **Significant changes for indirect admission patients after transfer** One-to-one nursing care reduced Falls reduced	Not described except for CAM at admission to establish diagnosis of delirium No significant differences between groups for potential confounders Trend toward more women in direct admission group p = 0.076 **N = 54** 61.1% 18.5% 16.7% 3.7% No significant difference between groups 42.6% 24.6% 18.0% **Indirect (54) vs direct admission (68)** **% or mean (SD) vs %, or mean (SD) OR, p** 63.0% vs 44.1%, OR 2.2, p = 0.038 75.9% vs 58.8%, OR 2.2, p = 0.047 40.0% vs 61.9%, OR 0.4, p = 0.047 25.5 (20.4) vs 17.3 (14.7), OR 8.3, p = 0.011 21.7 (19.9) vs 10.6 (11.5), OR 11.1, p <0.001 40.7% vs 58.8%, OR 0.4, p = 0.047 1.9% vs 1.5%, OR 1.3, p = 0.889 (NS) **Before vs after transfer to Unit** 12 (24.1%) vs 1 (1.9%), p = 0.002 14.2 vs 6.7 per 1000 delirium patient days	Possible reasons for better outcomes in the Unit for patients with hyperactive (or mixed) delirium -patients are unlikely to require transfer for management of behavioral disturbance or for general medical illnesses -adverse effects of transfer are avoided with possible -shorter LOS -lower use of restraints -better outcomes -more effective communication and integration of medical and psychiatric care -rapid assessment of behaviorally disturbed patients -rapid assessment of acute medical deterioration -nursing staff are dually qualified in medical and psychiatric conditions -the physical structure of the Unit enables close and persistent observation of delirious patient with hyperactive symptoms (especially psychomotor agitation) allowing early intervention and management of risk factors -the secure area prevents wandering and reduces the need for 1:1 nursing care
		n = 68 direct admission from ED Men and women (67.6%) Mean age 81.0 (6.9) Hyperactive delirium (80.9%) Residing at home (61.8%) Dementia (41.2%) Wanderer (57.4%) Charlson Comorbidity Index 1.8 (1.3) Patients admitted directly to the Unit within 24 h of presentation	**Delirium assessment:** **Baseline characteristics** **Primary outcomes**	See above See above See above	

Conclusion: Delirious patients with hyperactive symptoms admitted directly from the emergency department showed better outcomes and shorter length of stay that those transferred from other wards to this secured behavioral unit jointly used by geriatricians and pyschogeriatricians. Transferred patients received better management and had fewer accidents in this unit.

QUALITY / RISK OF BIAS RATING WORKSHEET

Evidence Ratings [adapted based on Cochrane risk of bias (top 6 items only), Jadad scoring and Lancet review approach Inouye et al]	**Quality Score 1 or 0 [include notes for any 0s]**	**Risk of Bias Rating (Low; Unclear, High) [include notes on interpretation]**	**Notes for 0 Quality Scores and Risk of Bias Interpretation**
1. **Balanced allocation (1 point if achieved)**: o Description of the method used for balanced allocation in sufficient detail to allow an assessment of whether it should produce comparable groups. This will typically include either a valid randomization procedure or prospective individual matching between intervention and control groups. o Evidence that balance was achieved	0	High	No significant difference between study groups, but no matching
2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	Unclear	Attempts were made to avoid observational bias in data collection
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	0	High	NA-retrospective study
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	1	Low	
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	Unclear	Historical study groups Investigators reported analyzing data to control for potential bias in the study design/ confounders Funding not described
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	1		
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 4**

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REVISED 11/11/13

G5-Goldberg SE, Bradshaw LE, Kearney FC, et al. Care in specialist medical and mental health unit compared with standard care for older people with cognitive impairment admitted to general hospital: randomised controlled trial (NIHR TEAM trial). BMJ. 2013;347:f4132.

Study Characteristics	Population	Intervention Groups	Results		Comments
			Measure	Outcome	
Goldberg SE 2013 UK **Setting** University Hospital – Combined medical and mental health unit for older people **Study Design** RCT **Randomization method** Identified in acute admission unit; included patients randomized 1:1 to intervention/control groups using a computerized log; Blinded clinical staff but research staff not blinded **Study Length/Start-Stop Dates** 7/2010 – 12/2011 **Purpose** To evaluate the combined medical and mental health unit (specialist unit) to determine improved outcomes, experience, and satisfaction compared with standard care **Funding source(s):** UK National Institute for Health Research Grant **Quality Score** 3 **Risk of Bias**: High	**N = 884 randomized** (10 randomized twice) n = 437 specialist unit n = 437 standard care **Excluded after randomization** n = 130 specialist unit n = 147 standard care (See Figure 1 in PDF for detail) **Inclusion** Age ≥65 Identified as "confused" by physician at admission Family member or other carer available to participate Informed consent -patient if capacity present -carer if capacity not present **Exclusion** N = 277 (see PDF) Critical care required Surgery required Stroke admitting diagnosis Patients admitted to medical wards not randomly allocated **Protocols – all patients** Standard medical care Standard mental health services Rehabilitation Intermediate and social care No use of physical restraints **Data collection/ assessments** Trained researcher (s) interviews Medical and nursing notes DEMQOL EuroQoL EQ-5D Charlson Comorbidity Index Medication history Dementia care mapping (2 trained researchers) -observations every 5 minutes for 6 h per patient Process of care assessed -2 senior geriatricians Blinded RAs completed outcome assessments Follow up = carer interviews 90 (7) days after randomization Other – see PDF p 3 of 12	**n = 310 specialist unit** Men and women (56%) Median age 85 (80-88 **Medical and mental health unit** 28 bed specialist unit Core protocols = geriatric medical ward 5 enhanced components 1 specialist mental health staff -3 nurses -1 occupational therapist -2 x week psychiatrist consultant -additional physiotherapy, speech and language therapy -3 healthcare assistants (activities) 2 staff trained in recognition and management of delirium and dementia and person-centered dementia care 3 program of organized therapeutic and diversionary activities 4 environment made more appropriate for people with cognitive impairment 5 proactive and inclusive approach to family carers was adopted Discharge letters to family doctors and other community services Delirium prevention actively initiated for known risk factors	**Delirium assessment:** DRS-R-98 **Baseline characteristics** Care home resident Median DRS score Categorical delirium (DRS >17.75) Previous paralysis or hemiparesis Previous hip fracture **Primary outcomes** Process of care Days spent at home Return home from hospital Overall mortality Move to care home Readmissions **Secondary outcomes**	Not described (reported in text/table, but not described **Significant differences between groups Specialist (310) vs standard care (290)** 28% vs 21%, p 0.03 19 (11-27) vs 20 (14-27) p 0.03 53% vs 62%, p 0.02 4% vs 10%, p 0.01 14% vs 7%, p o.01 **Significant differences between groups** P <0.05 on 42/132 intervention process items (See PDF Table 2) (See PDF Table 3) NS median 51 vs 45 days, p 0.3 NS 74% vs 70%, p 0.54 NS 22% vs 25% p 0.89 NS 29% vs 28% p 0.30 NS 32% vs 35%, p 0.31 See PDF Tables **Table 4**: (n = 46 vs 44) Non participant observer study data report on outcomes on the limited number of observations **Table 5** (n = 234 vs 228) Satisfaction outcomes are reported many of which are significant **Table 6**: 90 day follow up outcomes provide a number of significant comparisons, but it is not clear how many were in the follow up groups	**What this study adds:** Best practice acute hospital management of older people with delirium and dementia does not improve health status or reduce use of hospital resources. The experience of patients and satisfaction of family carers, however, are improved As many of these patients are approaching the ends of their lives, these are important outcomes Limitations -compromises in trial design may have introduced bias -patients were recruited and /or excluded after randomization -significant baseline imbalances -limited patients available for follow up -some data was missing
		n = 290 standard care Men and women (49%) Median age 85 (80-89) **Standard care (control)** 5 acute geriatric medical wards 6 general internal medicine wards **Geriatric medical wards** -comprehensive geriatric assessment -staff had general experience with delirium and dementia -mental health support provided on request from consulting psychiatrists	**Delirium assessment:** **Baseline characteristics** **Primary outcomes** **Secondary outcomes**	See above See above See above See above	
Conclusion: Specialist care for people with delirium and dementia improved the experience of patients and satisfaction of carers, but there were no convincing benefits in health status or service use. Patients' experience and carers' satisfaction might be more appropriate measures of success for frail older people approaching the end of life.					

QUALITY / RISK OF BIAS RATING WORKSHEET

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2. **Allocation concealment (1 point if achieved)**: o Description of method used to conceal the allocation in sufficient detail to determine whether the intervention allocations could have been foreseen before enrollment by either investigators or participants. Typically, this will be blinded enrollment.	0	High	Blinding variable according to role in study
3. **Blinded outcome assessment (1 point if achieved)**: o Description of methods used to blind study participants, investigators, and outcome assessors as to the study group.	1	Low	Outcome assessors described as blinded
4. **Completeness of outcome data (1 point if achieved)**: o Description of study attrition (withdrawals, deaths and dropouts), and any exclusions from the analyses. Reasons for all such attrition/exclusions should be reported.	0	High	Exclusions after randomization (>30%) Acknowledged missing data
5. **Selective outcome reporting (1 point if achieved)**: o All primary and secondary outcomes are reported. No evidence that one or more outcomes were not reported, or that additional outcomes (not pre-specified) are reported.	1	Low	
6. **Other sources of bias (1 point if achieved)**: o Problematic study design (historical controls, or before-after study) o Extreme baseline imbalances o Drug company sponsorship of study (or author(s) disclosed drug company relationship(s) o For observational studies: confounders inadequately controlled o For RCTs: lack of intention-to-treat (ITT) analysis: HIGH risk of bias if not present	0	High	Significant baseline imbalances Exclusions after randomization No ITT
OVERALL RISK OF BIAS (Low, Unclear , High) based on 1-6 above			**BIAS RATING = High**
7. **Validated delirium measure used (indicate which measure) (1 point if used)**:	0		DRS is validated but no description of delirium assessment
8. **Sample size ≥50 each study arm (1 point if achieved)**:	1		
TOTAL QUALITY SCORE (0-8)			**QUALITY SCORE = 3**

Instructions on rating:

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